Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Representative Selection of Studies of ASD Heritability.

	Twin Study	Family Study	Other
Selected studies	Steffenburg et al., 1989[1] Bailey et al., 1995[2] Le Couteur et al., 1996[3] Ronald et al., 2006[4] Taniai et al., 2008[5] Lichtenstein et al., 2010[6] Hallmayer et al., 2011[7] Nordenbæk et al., 2014[8] Frazier et al., 2014[9] Colvert et al., 2015[10]	Sandin et al., 2014, 2017[11,12] Yip et al., 2018[13]	Gaugler et al., 2014[14] Pettersson et al., 2018[15]
Population	Nordic regions (Denmark, Sweden, Finland, Iceland, Norway), United Kingdom, Japan, United States	Sweden	Sweden
Statistical method	Multifactorial threshold model (Falconer, 1965); Tetrachoric correlation; structural equation models	Liability-threshold models	SNP-based heritability*
Sample size, minimum-maximum	Pairs: 21-7,982	Individuals: 776,212 - 2,049,973	Individuals: 3,046 - 46,350 SNPs: 46,350 - 531,906
Heritability estimate, minimum-maximum	21% - 99%	83% - 84.8%	12% - 52.4%

Notes: * The SNP-based estimates can only provide a lower bound for the heritability[16].
Studies in this table were selected based on the authors' knowledge only and should not be considered as a full systematically reviewed.

eAppendix 1: Cohort Population, Outcome Ascertainment and Covariates Information

Cohort population

The study cohort was created by including live born singletons identified from medical birth registers in five countries: Denmark, Sweden, Finland, Israel, and Western Australia. For Denmark, Sweden, Finland and Western Australia, we included all births between 1st January 1998 and 31st December 2007. For Israel we included all live births between 1st January 2000 and 31st December 2011 from offspring of a Jewish cohort including all persons born 1922 to 1947 and who immigrated to Israel from Europe after 1945[17]. We excluded twins and multiple births because we did not have information about their zygosity. In Sweden, we obtained information about which individuals were full, half siblings, or cousins from the Swedish Multi-Generation Register[18]. For Denmark[19,20], and Finland[21,22] corresponding information was derived from the Medical Birth Registers, and for Western Australia[23,24] from the Western Australia Birth Registry. For Israel, we identified sibling relations and cousins from a cohort including all persons born 1922 to 1947 and who immigrated to Israel from Europe after 1945[17], made available by the 'Family Registry' of the Israel Ministry of the Interior.

Outcome ascertainment

Denmark, Finland, Sweden and Israel provided clinically ascertained diagnoses from national patient registers while the data from Western Australia was obtained from a government provided service and benefits register with clinically ascertained autism diagnoses. The individuals were followed for a diagnosis of ASD from birth up to 31-Dec-2014 in Sweden, 31-Dec-2013 in Denmark, 31-December-2012 in Finland, 31-December-2014 in Israel, 01-July-2011 in Western Australia. Case ascertainment, and details on the reliability and validity of reported diagnoses have been published previously for all included populations[25].

ASD and AD code assignment for MINERvA network:
If multiple codes are specified for a child, the code selected on the basis of the algorithm:

- if ever Rett's or Childhood Disintegrative Disorder (CDD), then assign Rett or CDD
- if never Rett's or CDD, then
    - AD: Autistic disorder is subtype if EVER received this diagnosis (disregard other ASD subtype diagnoses)

- Asperger's: If NEVER AD AND ever had Asperger disorder, then assign ASPERGER'S DISORDER (ASP) diagnosis (disregard other ASD subtypes)
- PDD-NOS: if NEVER AD, and NEVER ASP, and EVER (PDD-NOS OR ATYPICAL OR OTHER PDD) then assign PDD-NOS
- If assigned both International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes, then assign ICD-10 code

If the classification derives from educational sources and does not reflect an ICD/DSM diagnostic code: set ASD_CODE to the most specific diagnosis according to hierarchy above, choosing the most specific diagnosis supported by the system using the following codes: Autism (general ASD) = 999.0, Autistic Disorder =999.1, PDD-NOS=999.2, Asperger's =999.3. Set ASD type unknown.
Children with no qualifying diagnosis of ASD or AD will be assigned ASD=0.

Covariates

We obtained information about year of birth and sex of the child from the medical birth registers in Sweden, Denmark and Finland and from the Ministry of the Interior in Israel. In Western Australia, the information comes primarily from the Western Australia Midwives Notification System and from the Western Australia Birth Registry[23,24] when data was missing in the former. We reported and compared birth year in two cohorts: 2003-2007 vs. 1998-2002 except for Israel, we reported and compared birth year cohort 2006-2011 vs. 2000-2005. Israel sample is different from other countries as it's followed-forward from the origin cohort and selected their offspring born between 2000 and 2011, which has low missing information on relativeness relations.

eTable 2. Data Source and Outcome Ascertainment Information across Sites.

	Denmark	**Finland**	**Sweden**	**Israel**	**Western Australia**
Data source	Medical Birth Registers	Medical Birth Registers	Swedish multi-generation register	'Family Registry' of the Israel Ministry of the Interior and Ministry of Health	WA Birth Registry
Source population	All births between 1st January 1998 and 31st December 2007	All births between 1st January 1998 and 31st December 2007	All births between 1st January 1998 and 31st December 2007	All births between 1st January 2000 and 31st December 2011 from offspring of a cohort including all persons born 1922 to 1947 and who immigrated to Israel from Europe after 1945	All births between 1st January 1998 and 31st December 2007
Follow-up date for diagnosis	31-Dec-2013	31-Dec-2012	31-Dec-2014	31-Dec-2014	01-July-2011
Diagnosis system	1969-1993: ICD-8; 1994-2013: ICD-10	1987-1995 ICD-9; 1994-2014 ICD-10	1987-1997: ICD-9, from 1997: ICD-10	Before age 3: In-person diagnosis is made by child psychiatrists or pediatric neurologists with an expertise in neurodevelopmental disabilities[26]. After age 3: DSM-V (after 2013)/DSM-IV (before 2013) plus a committee with an expert plus various psychometric test[27].	Before 1994: DSM-IIIR; 1994-2000: DSM-IV; 2000-2014: DSM-IV-TR

Note: WA: Western Australia; ICD: International Statistical Classification of Diseases; DSM: Diagnostic and Statistical Manual of Mental Disorders.
For Sweden, diagnosis was given by treating physician, usually a specialist with child psychiatry.
For Israel, using of DSM-V/DSM-IV is depended on clinical impression.

eTable 3. ASD Diagnoses under Various Diagnostic Systems and MINERvA Categories.

Diagnostic System	**ICD-8**	**ICD-9**	**ICD-10**	**DSM-IV**
Associated Codes	299.00/01/02/03 (Psychosis; used in Denmark to indicate autism)	299.0 (Infantile Autism) 299.1 (Childhood disintegrative psychosis) 299.8 (Other) (note: should include Asperger Syndrome and Other PDD) 299.9 (unspecified) (note: should include PDD-NOS).	F84.0 (Childhood Autism) F84.1x (Atypical Autism) F84.5 (Asperger Syndrome) F84.8 (Other PDD) F84.9 (PDD-NOS) F84.2 (Rett Syndrome) F84.3(Childhood Disintegrative Disorder (CDD)	299.1 (Autistic Disorder) 299.2 (Childhood Disintegrative disorder (CDD)) 299.8 (Rett Syndrome) 299.8 (Asperger Syndrome) 299.8 (PDD-NOS)
MINERvA CODE	299.00 (AD) 299.02 (ASP) 299.01/03 (PDD-NOS)	299.0 (AD) 299.8 (ASP) 299.9 (PDD-NOS)	F84.0 (AD) F84.5 (ASP) F84.9/F841.x/F84.8 (PDD-NOS)	299.0 (AD) 299.8 (ASP) 299.8 (PDD-NOS)
MINERvA ASD_TYPE	0 (No ASD) 1 (AD autistic disorder) 2 (Asperger) 3 (PDD-NOS) 4 (ASD type unknown)	0 (No ASD) 1 (AD autistic disorder) 2 (Asperger) 3 (PDD-NOS) 4 (ASD type unknown)	0 (No ASD) 1 (AD autistic disorder) 2 (Asperger) 3 (PDD-NOS) 4 (ASD type unknown)	0 (No ASD) 1 (AD autistic disorder) 2 (Asperger) 3 (PDD-NOS) 4 (ASD type unknown)

eAppendix 2: Statistical Methods

Statistical models

We used Generalized Linear Mixed Effect Models (GLMM)[28] to estimate genetic and environmental effects on the liability for Autism Spectrum Disorder (ASD) and Autistic Disorder (AD). As mentioned in the main text, the unit of analysis is the four types of 'families' defined by relativeness. For a 'family' i among the total number of 'families' (N) of our study, let $y_i \equiv (y_{i1}, \dots, y_{in_i})$ be the vector of binary outcomes n_i (up to six) members, for $\mathrm{i} = 1, \dots, \mathrm{N}$. All 'families' are assumed to be independent. Let $x_i, \dots, x_N$ be the covariate matrices for each family, each of size $n_i \times p$, where p is the probability. Conditional on the random effect b_i, we assume y_{ij} to be an independent Bernoulli event with probability p_{ij}, following:

$$\Phi^{-1}(p_{ij}) = x'_{ij}\beta + z'_{ij}b_i \qquad (1)$$

where β is a p-vector of intercept and fixed regression parameters (sex and birth year cohort in this study). The random parameter b_i captures the dependencies between members in the 'family'; the design vector z_{ij} shows the contribution of b_i to the outcome and $\Phi()$ is the normal distribution function. We assume b_i to be normally distributed with mean zero and variance $D_i(\theta)$, where θ contains all the variance component parameters.

In the saturated model, we separated the genetic and environmental effects into four variance components: A_i - the additive genetic effect, C_i - the shared environmental effect, M_i - the maternal effect, and e_i - the non-shared environmental effect (error residuals):

$$\Phi^{-1}(p_{ij}) = x_i\beta + A_i + C_i + M_i + e_i \qquad (2)$$

where $A_i \sim N(0, \sigma_A^2 R_A)$, $C_i \sim N(0, \sigma_C^2 R_C)$, $M_i \sim N(0, \sigma_M^2 R_M)$ and $e_i \sim N(0, \sigma_e^2 R_e)$; σ^2 denotes variance component for each random effect, and R denotes respective the correlation matrix for each component. We assumed independence for each effect and between different 'families'. The correlation structure for each component is illustrated in **eTable 4**. Details on how to generate the correlation matrices and examples see Pawitan et al.[29]. We assumed full siblings share half of their genes, so the correlation coefficient is 0.5 for full siblings, 0.25 for half siblings, and 0.125 for cousins. Half cousins were excluded from our analytic sample because their relationship coefficient of additive genetic may

vary from 0.015 to 0.125 by specific relationship. We defined the shared environmental effect as the effect of unique environment created by the parents for all of their children, so the relationship coefficient of shared environmental effect is 1 for full siblings and maternal half siblings, and 0 for paternal half siblings and cousins. An assumption behind this approach is that children lived with their mothers after a divorce and separation from the father, an assumption frequently made in these types of models; this is also the rationale of excluding half-siblings in our analytic sample.

For the maternal effect[30], we aimed to estimate the liability contributing from each maternal phenotype by assuming a relationship coefficient of 1 for full siblings and maternal half siblings, 0.5 for maternal parallel cousins, and 0 for other types of cousins and paternal half siblings. Non-shared environmental effects were residuals, which represent the unique risk factors exposed by each individual, the correlation coefficient is 0 for all relativeness pairs and $\sigma_e^2 = 1$ for ease of calculation.

eTable 4. Assumed Genetic and Environmental Correlations between Relative Pairs

Pair type		**Variance component**		
	Additive Genetic Effects	Shared Environmental Effects	Maternal Effects	Non-shared Environmental Effects
Full sibling	0.5	1	1	0
Maternal Half Sibling	0.25	1	1	0
Paternal Half Sibling	0.25	0	0	0
Maternal Parallel Cousin	0.125	0	0.5	0
Other Cousin	0.125	0	0	0

To illustrate how the correlation matrices are calculated, we give an example of a 'maternal parallel cousin family' with four children (two from each nuclear family) whose mothers are sisters. For the saturated model (ACME model), the correlation matrices can be written as:

$$R_A = \begin{pmatrix} 1 & 0.5 & 0.125 & 0.125 \\ 0.5 & 1 & 0.125 & 0.125 \\ 0.125 & 0.125 & 1 & 0.5 \\ 0.125 & 0.125 & 0.5 & 1 \end{pmatrix};\ R_C = \begin{pmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{pmatrix};$$

$$R_M = \begin{pmatrix} 1 & 1 & 0.5 & 0.5 \\ 1 & 1 & 0.5 & 0.5 \\ 0.5 & 0.5 & 1 & 1 \\ 0.5 & 0.5 & 1 & 1 \end{pmatrix}\ R_e = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

For model (1), marginal probability will be calculated as:

$$P(Y_i = y_i|x_i) = \int p(y_i|x_i, b_i)|D_i(\theta)|^{-q/2} \exp\left\{-\frac{1}{2} b_i' D_i(\theta)^{-1} b_i\right\} db_i$$

$$= E_{b_i}\left\{\prod_j p_{ij}^{y_{ij}} (1 - p_{ij})^{1-y_{ij}}\right\}$$

$$= P(l_{ij} < V_{ij} < u_{ij}) \text{ for jth 'family' structure, } \quad (3)$$

where q is the dimension of b_i, $V_{ij} \equiv Z_j - z_{ij}' b_i$ (Zj's are independent standard normal variates). The upper bound $u_{ij} = \begin{cases} x_{ij}'\beta\,, if\, y_{ij} = 1 \\ \infty, \quad if\ y_{ij} = 0 \end{cases}$ and lower bound $u_{ij} = \begin{cases} -\infty, \quad if\, y_{ij} = 1 \\ x_{ij}'\beta\,, \ if\ y_{ij} = 0 \end{cases}$.

In our primary analysis, we aggregated 'families' by the configuration of family size, family type, sex, birth year cohort and ASD outcome, so there are M unique family configurations, and w_j 'families' with the same configuration j=1, 2…, M.

Let $f_i(y_i, x_i, \beta, \theta) \equiv P(Y_i = y_i|x_i)$,

$$l = \sum_{i=1}^{N} \log f_i(y_i, x_i, \beta, \theta) = \sum_{j=1}^{M} w_j \log f_j(y_j, x_j, \beta, \theta),$$

A Monte-Carlo algorithm was employed to compute the probability in (3) for evaluation, and variance component estimates for each random effect was optimized correspondingly[31,32]. Likelihood based two-sided 95% confidence intervals were obtained for each component; lower (σ_L^2) and upper (σ_U^2) bounds were used to calculate 95% confidence intervals for the fraction of variation explained.

The fraction of variation explained by i'th random effect and its conservative two-sided 95% confidence interval is calculated as $\frac{\sigma_i^2}{\sigma_i^2 + \sum_{j \neq i} \sigma_j^2}$ ($\frac{\sigma_{iL}^2}{\sigma_{iL}^2 + \sum_{j \neq i} \sigma_{jU}^2}$, $\frac{\sigma_{iU}^2}{\sigma_{iU}^2 + \sum_{j \neq i} \sigma_{iL}^2}$) and so be skewed due to transformation. Heritability, in this case, was estimated as $h^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_C^2 + \sigma_M^2 + \sigma_e^2}$ (two-sided 95% confidence interval: $\frac{\sigma_{AL}^2}{\sigma_{AL}^2 + \sigma_{CU}^2 + \sigma_{MU}^2 \sigma_e^2}$, $\frac{\sigma_{AU}^2}{\sigma_{AU}^2 + \sigma_{CL}^2 + \sigma_{ML}^2 \sigma_e^2}$), where $\sigma_e^2 = 1$ for the saturated ACME-model[33].

In our model, shared environmental effect is assumed to capture all environmental risk created by the children's parents, so it is only shared by full siblings – not by cousins. 'Maternal effect' is used to describe the association between maternal phenotype with offspring's ASD/AD[13].

The coefficient of additive genetic correlation was assumed to be 0.5 for full siblings and 0.125 for cousins[29,34]. We assumed the shared environmental correlation to be 1 for full siblings and 0 for cousins. We assumed the correlation coefficients of maternal effect to be 1 for full siblings, 0.5 for maternal parallel cousins (mPC) and 0 for other types of cousins. Our saturated model (Generalized Linear Mixed Model[28]) can be written $Probit(p_i) = x_i\beta + A_i + M_i + C_i + e_i$ with Gaussian random effects of additive genetic $A_i \sim N(0, \sigma_A^2)$, maternal $M_i \sim N(0, \sigma_M^2)$, shared environment $C_i \sim N(0, \sigma_C^2)$ and a residual term (usually labeled 'non-shared environmental effect') $e_i \sim N(0, \sigma_e^2)$. x_i is the matrix for the fixed covariates and β is the corresponding vector of parameters. For each country, the categorical covariates sex (male vs. female), birth year cohort (2006-2011 vs. 2000-2005 for Israel and 2003-2007 vs. 1998-2002 for all other countries) were included as fixed factors.

Additionally, we fitted two models with data combined from: 1) the Nordic countries since they are similar with respect to health systems and reporting registers; and 2) the Nordic countries plus Western Australia, all countries that could be combined. A third fixed parameter for country was added to the pooled models. The heritability (h^2) can be calculated as fraction of the total variation explained by variance component of additive genetic (A): $h^2 = \frac{\sigma_A^2}{\sigma_A^2+\sigma_M^2+\sigma_C^2+\sigma_e^2}$.

Instead of relying on assumptions of estimates following an asymptotic normal distributions we calculated two-sided 95% confidence intervals using profile likelihood methods [31]. We used R[35] version 3.1.2 (2014-10-31) on a Linux RedHat version 6.0 64-bit server for all calculations except Israel (R version 3.4.0 (2017-04-21)).

Analytic Sample Ascertainment

Structured families

Paired cousin families: We divided the paired cousin families into cousins related through mothers, the maternal parallel cousins (mPCs), and other full cousins (paternal parallel cousins - pPCs and cross cousins - CCs)[13]. Only mPCs were identified separately because coefficient matrices of maternal effect only differ between mPCs and other full cousins. If there were included.

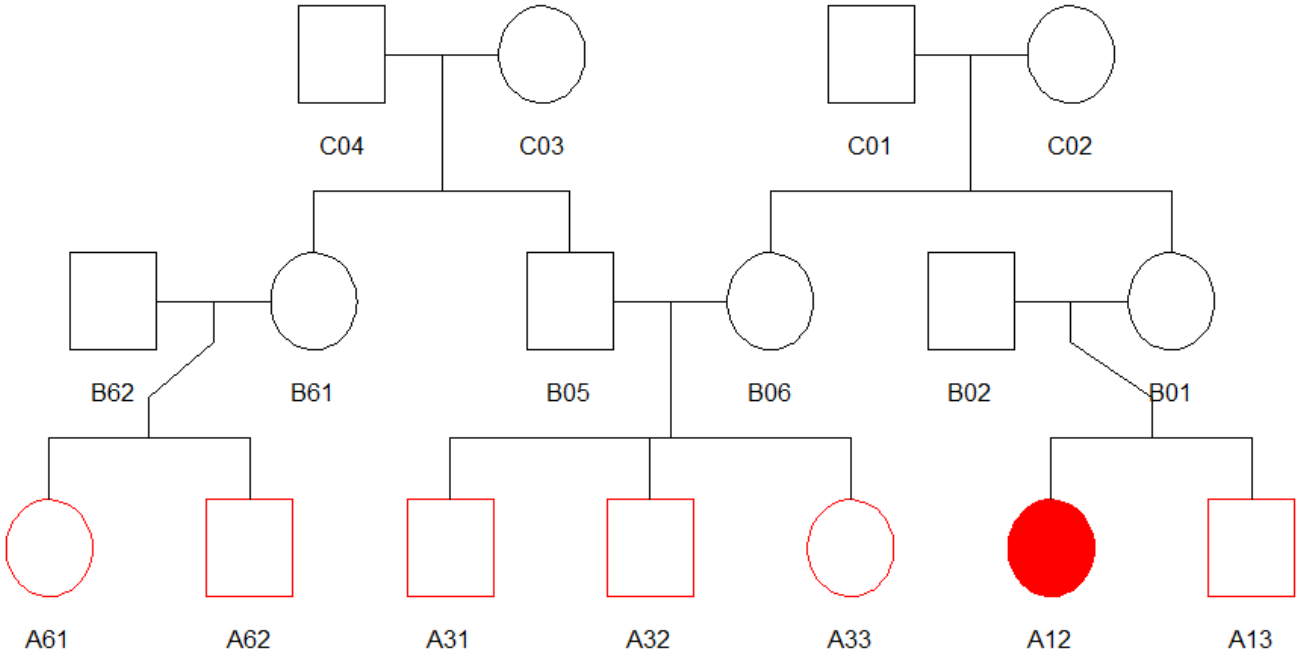
Unpaired cousin families: The unpaired families were formed by full siblings who did not have any cousins identified.

We also applied some exclusions: *Half cousins*, i.e. children whose parents are half siblings, were excluded from the analytic sample because complex relativeness including exposure for additive genetic and maternal effects. Furthermore, we did not include maternal and paternal *half siblings* because models including half siblings would require assumptions that children did or did not live with their mothers or father. Moreover, even if this was indeed known, it would be difficult to distinguish maternal effects from shared environmental effects using half and full siblings only. An analysis similar to ours, using a large Swedish cohort (overlapping with our cohort) showed that estimates with and without half siblings are similar[13].

Three generation pedigree

As described in the **'Analytic samples and statistical models'** section from the main manuscript, we started with family pedigrees of three generations by identifying parent's identification of cohort children and all available individuals from the registry. In a pedigree plot, black outline represents individuals outside the cohort and red represents in the cohort; square shape represents male and circle represents female, red filling represents positive diagnosis of ASD; within each generation, individuals are ordered from left to right by descending age. Exemplar **eFigure 1** shows a three-generation family's pedigree, for which all the third generation (A-generation) children are in the cohort (red outline) and one child A12 gets ASD (generated in kinship using R). In this example, among the second generation (B-generation), parent's identification is not available for individual B62 and B02, while B61 and B05 are sister and brother, B06 and B01 are sisters.

eFigure 1. Analytic Sample Ascertainment - Example 1.

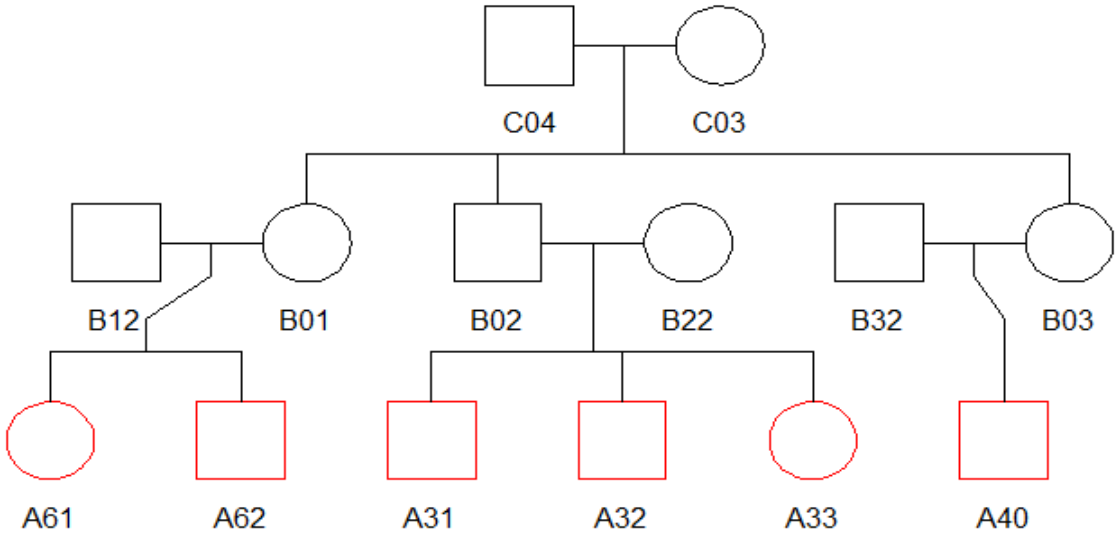


Truncation and replication during family structure construction

Our liability model, as described above, requires specific data structure. The analytic unit is 'family' defined in the **Methods-Analytic samples and statistical models** section in the manuscript. It could be a 'paired cousin family' with children from two nuclear families, or an 'unpaired family' with full siblings only. To form such structured 'family', there are inevitable truncations and potential replications of children during sample data construction. Here we list as many scenarios as we anticipated and give examples to illustrate our procedure and potential pitfalls.

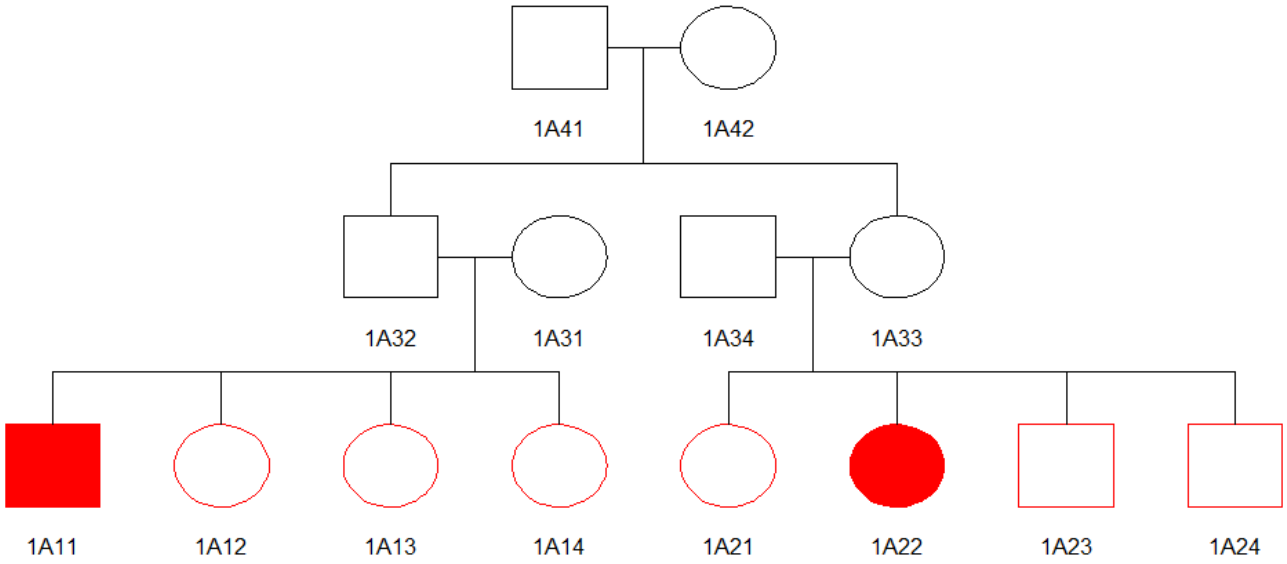
1) Data truncation due to more than two full siblings at second (parents') generation. For calculation purpose, each 'family' contains cousins from at most two nuclear families, truncation has been made to achieve such 'families' without been affected by family size at the parents' generation. In exemplar **eFigure 2**, individuals B01, B02, B03 are full siblings, and all A-generation children are in cohort; however, to construct 'family' for analysis, we only select children of the oldest two full siblings, i.e., individuals A61, A62, A31, A32 to form a 'paired cousin family'. This introduces data truncation of children from such families.

eFigure 2. Analytic Sample Ascertainment - Example 2.



2) Data truncation due to exceeding maximum number (n=6) of children for each 'family'. For families of large size, say more than three children from both nuclear families, we included three children from each nuclear family to minimize the size difference between the two nuclear families. In exemplar **eFigure 3**, child 1A14 and 1A24 were excluded from the analytic sample even though they were in cohort, and we selected three children from each nuclear family instead of two from the first and four from the second, or other combinations.

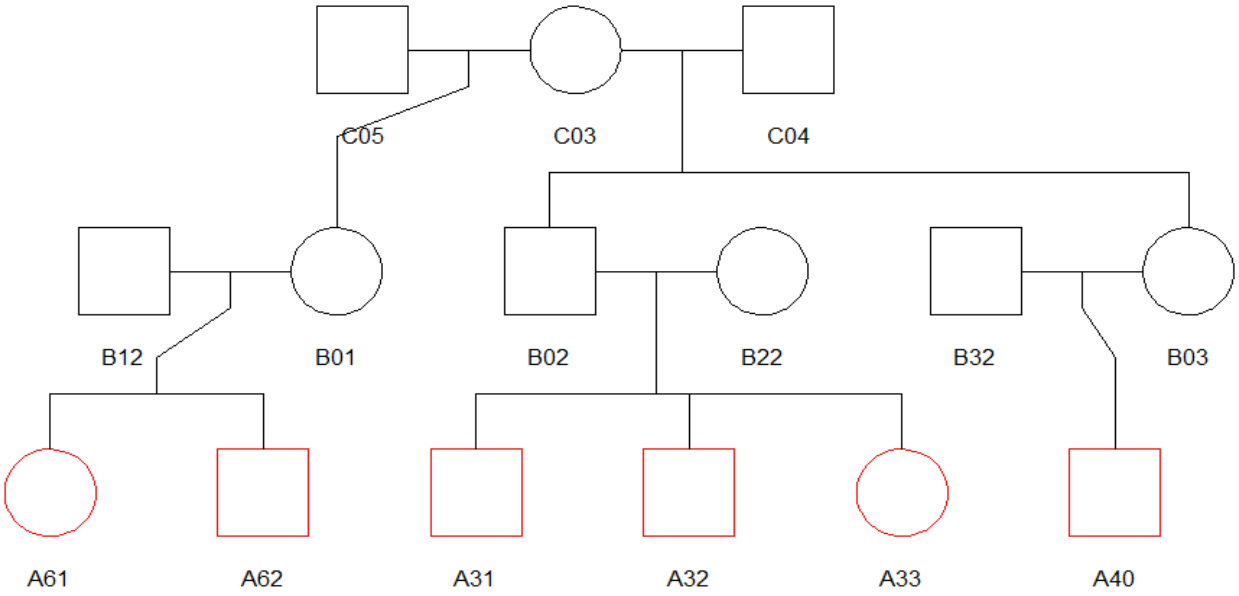
eFigure 3. Analytic Sample Ascertainment - Example 3.



3) Data truncation due to half siblings among second (parents') generation, i.e., half cousins. Half siblings at parents' generation were excluded, child/children of one mother/father were randomly selected as potential parents of analytic sample. In exemplar **eFigure 4**, subject B01

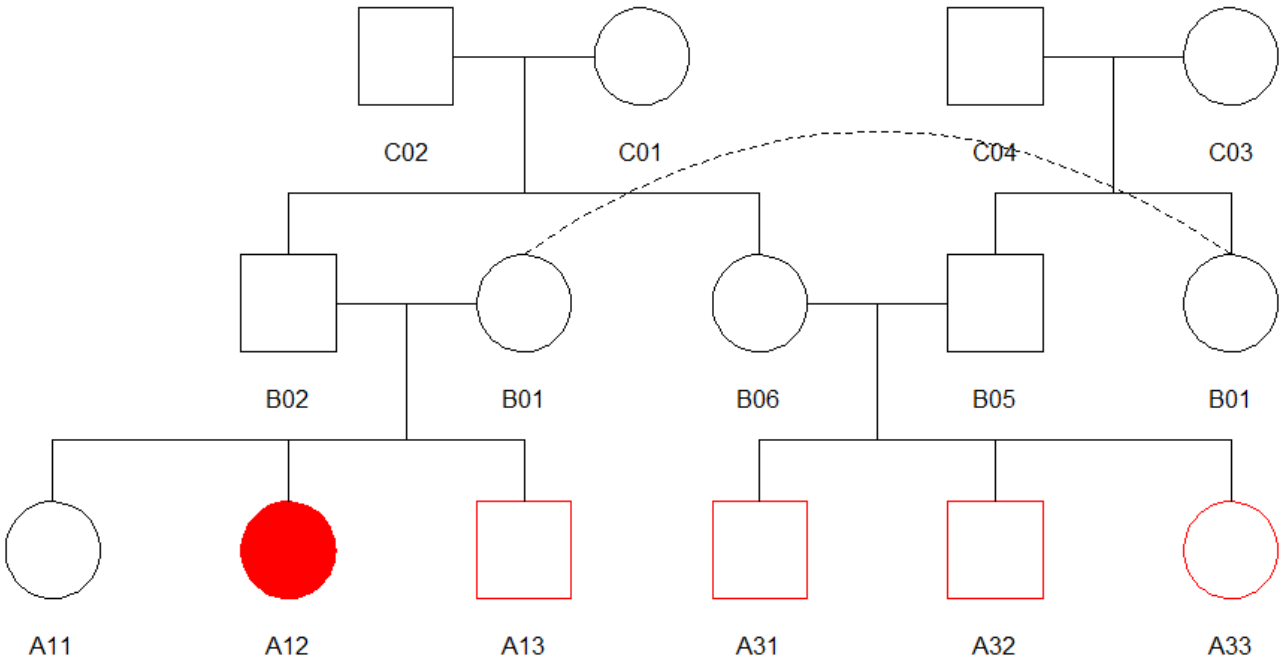
was selected because the ID number of her father (C05) is larger than father of the other nuclear family (C04). Children A31, A32, A33, A40 were excluded from analytic sample.

eFigure 4. Analytic Sample Ascertainment - Example 4.



4) Data replication due to relatedness of maternal and paternal lines. A child can have cousins from maternal and paternal side, so one can appear at most twice in our analytic sample. As defined 'family' was the minimum analysis unit in the liability model, we considered that replication of such cohort children won't affect independence of each sibling pair family. In exemplar **eFigure 1**, children A31, A32, A33 appeared twice in two 'paired cousin families': once is with their paternal cousins A61 and A62, the other time is with their maternal cousins A12 and A13.
5) Data replication due to 'double in-law marriage', i.e., a pair of siblings marries another pair of siblings. In examplar **eFigure 5**, subjects B01 and B05, B02 and B06 are two pairs of brothers and sisters, B01 married B02 and B05 married B06. In this situation, cohort children A12, A13, A31, A32, and A33 appeared twice in two identical 'paired cousin families'. This situation is considered very rare and would not affect our model results in significant ways.

eFigure 5. Analytic Sample Ascertainment - Example 5.



6) Data replication owing to 'sister marries brother'. This case is very extreme and rare, only two families were identified across all sites and excluded from analysis.

Statistical programs

We used R[35] version 3.1.2 (2014-10-31) on a Linux RedHat version 6.0 64-bit server for all calculations except Israel (R version 3.4.0 (2017-04-21) on a Linux/GNU 64-bit server through Ubuntu 16.04). In particular, we used the packages data.table[36] and reshape[37] for data management and transposition, lme4[38] for generalized linear regression, mvtnorm[39,40] to generate multi-normal distribution, survival[41,42] to construct and plot inverse Kaplan-Meier curve, and ggplot2[43] for general plotting.

eAppendix 3: Sensitivity and Complementary Analyses

We performed three sensitivity analyses. For Finland and WA, which had a small number of concordance pairs, we re-fitted the **ACE** model using half siblings instead of cousins. Since a lower prevalence could affect the heritability estimates[44,45], we used data simulation reducing the number of ASD cases in the Swedish analytic sample to approximate prevalence rates in Finland and refitted the **ACE** model (see: **eAppendix 3-Simulation**). To illustrate the model robustness, we plotted the country specific likelihood functions of additive genetic (A) and shared environmental effect (C) for the **ACE** models (**eFigure 17**).

We performed an extensive set of analyses to test the robustness of our results. Since the analytic sample used for the statistical models did not include the entire study cohort, we performed additional analyses (e.g., comparisons in characteristics associated with ASD/AD between different family pairs) to ensure that the analytic sample was representative of the study cohort (**eTable 9-11**). We also compared age-specific outcome ascertainment and follow-up pattern between countries by constructing country specific inverse Kaplan-Meier curves for ASD and AD assuming independent censoring (**eFigure 10-11**).

Sensitivity analyses

Finland and Western Australia had a small number of concordant cousin pairs, and we therefore re-fitted the **ACE** model using half-siblings instead of cousins (**eTable 5**).

Simulation

To study the impact of ASD prevalence on model estimation, we randomly reduced the Swedish ASD prevalence to match the ASD prevalence in Finland in the cohort population. We chose Sweden as our sample cohort and ASD as the outcome because it had the largest sample size to tolerance losing cases. In the simulation, if the heritability estimate goes down and/or shared environmental effect increases, it will support arguments proposed by Tick et al.[45] in their meta-analysis for autism and Sullivan et al.[44] for schizophrenia, and partially explain why Finland has lower heritability estimates.

Simulation procedure:

1) In the cohort population, calculate prevalence for Sweden (P0S) and Finland (P0F), and their ratio R=P0F/P0S.
2) Generate a binomial distributed vector of 0 and 1 as PB=rbinom(NS,1,R), where NS is the number of children in Swedish cohort (rbinom is the R-function used for generating binomial data).
3) Multiply Swedish binary ASD status vector ASD and PB to ascertain ASD_New.

4) Use ASD_New as ASD outcome for analysis, i.e., construct an analytic sample again and run our primary ACE model.

In the simulation, we randomly remove some existing ASD cases without introducing new cases (only 1 => 0, no 0 => 1) to match Finnish prevalence and keep the Swedish ascertainment in most possible way. However, this simulation is potentially affected by factors such as family size and structure and random errors from one-time simulation, thus could not reflect the real situation for Finland. Results from the simulation are presented in **eTable 6**.

Complementary analyses

Genetic and Environmental Contributions to AD

We estimated genetic and environmental contributions to AD for Denmark, Finland, and Sweden only, because Israel did not have AD diagnosis and WA sample was too small (**Table 1**). Estimated heritability ranged between 79.5% and 84.6% in the AE model; 72.7% and 84.6% in the **ACE** model; and 74.4% and 79.0% for the **ACME** model. The heritability for the pooled Nordic countries samples ranged between 82.2% and 83.5% for the **AE**, **ACE** and **ACME** models (**eTable 8**, **eFigure 7**).

Country-specific point estimates of maternal effects ranged between 0.5% and 5.3% in the **ACME** model, and the pooled estimate was 0.6%, but in all models the confidence intervals included zero (**eTable 8**, **eFigure 14**).

Country-specific point estimates of shared environmental effect ranged between 0.4% and 10.6% in the ACE model; and 0.0%-0.6% in the **ACME** model. The estimates from the Nordic pooled sample were between 0.1% and 0.2% for the **ACE** and **ACME** models and the confidence intervals included zero (**eTable 8**, **eFigure 14**). The elevated estimate for Finland (10.6%) was only present in the **ACE** model and its corresponding two-sided 95% confidence interval was overlapped with the other countries.

Country-specific non-shared environmental effect estimates ranged between 14.8% and 20.5% in the **AE** model; 15.1%-21.9% in the **ACE** model; and 19.8%-20.3% for the **ACME** model. The Nordic pooled estimate ranged between 16.4% -17.0% (**eTable 8**, **eFigure 15**).

Since the analytic sample used for the statistical models did not include the entire study cohort, we performed additional analyses to ensure that the analytic sample was representative of the study cohort. First, we derived summary statistics of the cohort population (**eTable 9**). Then we calculated the ASD/AD-rate by age for the cohort population and the analytic sample for each country (**eFigure 8-9**).

We didn't include all risk factors in our liability model as we don't think it would affect the estimates of variance component. Nevertheless, we described the distribution of these variables in cohort population for cousins and full siblings, across countries for: inter-pregnancy interval, mother's marital status, maternal/paternal age at birth, education level, and psychological history (**eTable 10**).

Our results are based on comparisons of case concordance between cousins and full siblings; therefore, we examined factors (e.g., sex ratio, family size) with a potential to influence AD/ASD risk differently in these two groups of analytical samples (**eTable 11**).

eTable 5. Fraction of Variation Explained by Each Random Effect for Liability of Autism Spectrum Disorder (ASD) in Finland and Western Australia (WA): **ACE** Model, Using Half and Full Siblings.

Population	Random Effects (95% CI)		
	Additive genetic (A)	Shared environment (C)	Non-shared environment (E)
Finland	70.6% (46.5%, 86.2%)	9.4% (1.5%, 24.7%)	20.0% (11.3%, 36.5%)
WA	59.3% (0.3%, 86.0%)	22.8% (5.1%, 66.4%)	17.9% (7.9%, 63.0%)

Notes: WA: Western Australia; CI: confidence interval.

eTable 6. Comparison between Simulated Swedish Cohort Population with Lower Autism Spectrum Disorder (ASD) Prevalence and Finland: **eAppendix 2-Simulation.**

Characteristics for Cohort Population and Analytic Sample			
Population	**Prevalence (per 1,000) for cohort population**	**Prevalence (per 1,000) for analytic sample**	**Sex ratio for analytic sample**
Simulated Sweden	6.91	6.31	2.78
Finland	6.89	6.28	3.49
A + C + E Model Estimates			
	Additive genetic effect	**Shared environmental effect**	**Unshared environmental effect**
Population	**Variance Component (95% CI)**		
Simulated Sweden	1.66 (1.38, 2.44)	0.09 (0, 0.17)	1
Finland	1.61 (0.72, 3.97)	0.44 (0.24, 0.71)	1
	Fraction of Variation Explained (95% CI)		
Simulated Sweden	62.0% (54.1%, 70.9%)	0.7% (0.0%, 6.8%)	37.3% (27.7%, 42.0%)
Finland	50.9% (25.1%, 75.6%)	14.0% (0.0%, 28.6%)	33.6% (17.6%, 53.9%)

Note: CI: confidence interval.

eTable 7. Autistic Disorder (AD) Concordance Pairs by Genetic Relativeness in Analytic Sample.

Relativeness Type	Countries					Total
	Denmark	Finland	Sweden	Israel	Western Australia	
Cousins	18	2	20	NA	1	41
mPC	7	0	5	NA	0	12
Full Siblings	20	13	91	NA	15	139

Note: NA: not available.
Cousins: children (cousins and full siblings) in the 'paired cousin families'.
mPC: children (cousins and full siblings) in the 'families' based on maternal parallel cousin pairs.
Full siblings: full siblings from all four types of 'families' defined base on relativeness.

eTable 8. Autistic Disorder (AD): Estimated Variance Components and Associated Two-sided 95% Profile Likelihood Confidence Intervals. All Estimates Are Recalculated to 'Fraction of Variation Explained'.

Model and Population	Random Effects (95% CI)			
	Additive Genetic (A)	Shared Environment (C)	Maternal (M)	Non-shared Environment (E)
Model 1: A + E				
Country Specific				
Denmark	84.6% (78.1%, 88.5%)	N/A	N/A	15.4% (11.5%, 21.9%)
Finland	85.2% (78.9%, 89.0%)	N/A	N/A	14.8% (11.1%, 21.1%)
Sweden	79.5% (78.3%, 84.4%)	N/A	N/A	20.5% (15.6%, 21.8%)
Western Australia	Not Converged			
Nordic Countries Combined	83.3% (77.6%, 87.5%)	N/A	N/A	16.7% (12.5%, 22.4%)
Model 2: A + C + E				
Country Specific				
Denmark	84.6% (69.7%, 88.7%)	0.4% (0.0%, 11.2%)	N/A	15.1% (10.6%, 21.5%)
Finland	72.7% (54.2%, 81.0%)	10.6% (3.8%, 26.7%)	N/A	16.7% (13.0%, 24.5%)
Sweden	76.3% (62.3%, 83.0%)	1.8% (0.0%, 10.2%)	N/A	21.9% (16.0%, 30.6%)
Western Australia	Not Converged			
Nordic Countries Combined	83.5% (72.8%, 87.7%)	0.1% (0.0%, 5.5%)	N/A	16.4% (11.9%, 29.7%)
Model 2: A + C + M + E				
Country Specific				
Denmark	74.4% (53.4%, 82.3%)	0.0% (0.0%, 11.1%)	5.3% (0.0%, 16.1%)	20.3% (13.9%, 28.7%)
Finland	Model Not Applicable			
Sweden	79.0% (60.9%, 84.8%)	0.6% (0.0%, 8.6%)	0.5% (0.0%, 8.3%)	19.8% (13.8%, 27.8%)
Western Australia	Model Not Applicable			
Nordic Countries Combined	82.2% (69.6%, 86.4%)	0.2% (0.0%, 3.7%)	0.6% (0.0%, 4.9%)	17.0% (12.9%, 24.1%)

Notes:
CI: confidence interval; N/A: not applicable; Nordic countries: Denmark, Finland, Sweden.

Fraction of Variation Explained: proportion of total variance explained by each random effect (details see **eAppendix 2-Statistical models**).
Data from Israel was not used for AD analyses because AD diagnosis was not available.

eTable 9. Description of Cohort Population.

Outcome	Country					Total
	Denmark	Finland	Sweden	Israel	Western Australia	
Number of Children	626,246	552,061	949,927	224,198	252,482	2,604,914
Sex						
Male	321,275	282,661	489,041	115,551	128,951	1,337,479
Female	304,971	269,400	460,886	109,567	123,531	1,268,355
Ratio	1.05	1.06	1.06	1.05	1.04	1.05
Birth Cohort						
1998-2002	316,090	272,033	444,514	121,934	121,634	1,276,205
2003-2007	310,156	280,028	505,413	102,264	130,848	1,328,709
Ratio	1.02	0.97	0.88	0.93	0.93	0.96
Number of ASD cases	9,583	3,801	14,554	920	1,276	30,134
AD	3,623	933	6,355	NA	1,092	12,003
% of ASD	37.8	24.5	43.7	NA	85.6	NA
ASD sex ratio	3.58	3.61	2.79	4.68	3.91	3.21
Children with missing identification information: Count (%)						
Mother	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Father	14,868 (2.4)	7,532 (1.4)	9,821 (1.0)	0 (0)	11,547 (4.6)	43,768 (1.7)
Maternal grandparent	80,467 (12.8)	39,290 (7.1)	155,042 (16.3)	0 (0)	129,225 (51.2)	404,024 (15.5)
Paternal grandparent	101,997 (16.3)	52,763 (9.6)	168,857 (17.8)	6 (0)	141,014 (55.9)	464,637 (17.8)

Notes:
ASD: autism spectrum disorder; AD: autistic disorder; NA: Not available.
For Israel, we reported number of children born between 2000-2005 and 2006-2011.
Sex ratio: male: female ratio for ASD prevalence (per 1,000).
For grandparent, any missing of grandfather or grandmother was considered as missing grandparent.

eTable 10. Comparison of Cousins and Full Siblings in the Cohort Population.

Variable	Family type	Country			
		Denmark	Finland	Sweden	Western Australia
Average Maternal Age at Birth (year)	Cousins	30.19	29.71	29.83	29.04
	Full Siblings	30.04	29.54	29.74	29.73
	Ratio	1.00	1.01	1.00	0.98
Average Paternal Age at Birth (year)	Cousins	32.45	32.03	32.13	32.048
	Full Siblings	32.66	32.02	32.54	32.34
	Ratio	0.99	1.00	0.99	0.97
Median Inter-pregnancy Interval (month)	Cousins	23	23	36	21
	Full Siblings	22	19	30	18
	Ratio	1.05	1.21	1.20	1.17
Proportion of married/partnered mother at birth	Cousins	54.1%	90.3%	NA	91.1%
	Full Siblings	59.9%	92.4%	NA	94.8%
	Ratio	0.90	0.98	NA	0.96
Average Maternal Education Level	Cousins	NA	4.04	4.33	NA
	Full Siblings	NA	4.07	4.35	NA
	Ratio	NA	0.99	1.00	NA
Average Paternal Education Level	Cousins	NA	3.82	4.33	NA
	Full Siblings	NA	3.85	4.08	NA
	Ratio	NA	0.99	1.06	NA
Proportion of Maternal Psychological History	Cousins	11.1%	11.6%	15.5%	13.5%
	Full Siblings	11.0%	10.7%	14.5%	11.8%
	Ratio	1.01	1.08	1.07	1.14
Proportion of Paternal Psychological History	Cousins	15.5%	13.6%	11.0%	13.5%
	Full Siblings	14.4%	12.4%	10.8%	11.8%
	Ratio	1.08	1.10	1.02	1.14

Notes:
NA: not available.
Israel was not included in this table because the covariates information is not available.
Cousins: singleton children born between 1998-2007 with cousin(s) in the cohort, different from analyzing data structure.
Full siblings: singleton children born between 1998-2007 with full sibling(s) in the cohort, different from analyzing data structure.
Ratio: 'cousins' vs. 'full siblings' ratio.
Education level: 0=Pre-primary level of education, 1=Primary level of education, 2=Lower secondary level of education, 3=Upper secondary level of education, 4=Post-secondary non-tertiary, 5=First stage of tertiary education, 6=Second stage of tertiary education; valid range 0-6 (ISCED-97 CODES).

eTable 11. Comparison of Cousins and Full Siblings in the Analytic Sample.

Variable	Family type	Country				
		Denmark	Finland	Sweden	Israel	Western Australia
Sex ratio	**Cousins**	3.63	3.52	2.77	5.11	3.88
	Full Siblings	3.69	3.42	2.89	4.75	4.17
	Ratio	0.98	1.03	0.96	1.08	0.93
AD proportion of ASD	**Cousins**	35.4%	24.3%	40.7%	100%	82.4%
	Full Siblings	34.7%	23.2%	40.2%	100%	83.4%
	Ratio	1.02	1.04	1.01	1.00	0.99
Proportion of ASD cases born between 2003-07	**Cousins**	36.2%	34.4%	37.2%	49.0%	38.8%
	Full Siblings	36.7%	33.8%	37.5%	51.8%	38.5%
	Ratio	0.99	1.02	0.99	0.95	1.01
Average family size	**Cousins**	3.31	3.49	3.32	4.20	3.53
	Full Siblings	2.23	2.36	2.21	2.64	2.35
	Ratio	1.48	1.48	1.50	1.59	1.50
Average age difference	**Cousins**	4.36	4.36	4.34	6.05	4.42
	Full Siblings	3.35	3.30	3.18	4.63	3.18
	Ratio	1.30	1.32	1.37	1.31	1.39

Notes:
Sex ratio: male: female ratio for ASD prevalence (per 1,000).
Cousins: children from the 'paired cousin families'.
Full siblings: full siblings from the 'paired cousin families' and 'unpaired cousin families'.
Ratio: 'Cousins' to 'Full siblings' ratio.
AD: autistic disorder; ASD: autism spectrum disorder.
For Israel, we reported the proportion of ASD cases born between 2000-2005.
Age difference: largest age difference between cousins or full siblings.

eTable 12. Autism Spectrum Disorder (ASD): Liability Model Estimates - Variance Components.

Model and Population	Random Effects (95% CI)		
	Additive Genetic (A)	Shared Environment (C)	Maternal (M)
Model 1: A + E			
Country Specific			
Denmark	4.19 (2.86, 5.86)	N/A	N/A
Finland	4.20 (2.73, 5.88)	N/A	N/A
Sweden	5.27 (3.92, 7.38)	N/A	N/A
Israel	Not Converged		
Western Australia	Not Converged		
Nordic Countries Combined	4.78 (3.79, 6.12)	N/A	N/A
Model 2: A + C + E			
Country Specific			
Denmark	4.11 (2.91, 5.75)	0.00 (0.00, 0.19)	N/A
Finland	1.61 (0.72, 3.97)	0.44 (0.24, 0.71)	N/A
Sweden	5.62 (3.75, 7.82)	0.01 (0.00, 0.17)	N/A
Israel	6.63 (3.00, +∞)	0.01 (0.00, 0.30)	N/A
Western Australia	2.56 (1.28, 4.35)	1.20 (0.50, 2.21)	N/A
Nordic Countries Combined	4.65 (3.77, 6.08)	0.01 (0.00, 0.11)	N/A
Model 3: A + C + M + E			
Country Specific			
Denmark	3.83 (2.78, 5.36)	0.01 (0.00, 0.19)	0.02 (0.00, 0.28)
Finland	1.52 (0.65, 3.73)	0.42 (0.21, 0.67)	0.05 (0.00, 0.29)
Sweden	4.65 (3.45, 6.50)	0.00 (0.00, 0.17)	0.08 (0.00, 0.32)
Israel	Not converged		
Western Australia	Not converged		
Nordic Countries Combined	4.50 (3.60, 5.80)	0.02 (0.00, 0.10)	0.03 (0.00, 0.17)

Notes:
CI: confidence interval; Nordic Countries: Denmark, Finland, Sweden; N/A: not applicable.
Variance component for non-shared environmental effect (E) is not shown in the table as it was set to be 1.

eTable 13. Autistic Disorder (AD): Liability Model Estimates - Variance Components.

Model and Population	Random Effects (95% CI)		
	Additive Genetic (A)	**Shared Environment (C)**	**Maternal (M)**
Model 1: A + E			
Country Specific			
Denmark	5.48 (3.56, 7.67)	N/A	N/A
Finland	5.75 (3.74, 8.05)	N/A	N/A
Sweden	3.88 (3.60, 5.43)	N/A	N/A
Israel	N/A		
Western Australia	Not Converged		
Nordic Countries Combined	5.00 (3.46, 7.00)	N/A	N/A
Model 2: A + C + E			
Country Specific			
Denmark	5.16 (3.65, 7.86)	0.02 (0.00, 0.58)	N/A
Finland	4.36 (2.83, 5.32)	0.63 (0.25, 1.40)	N/A
Sweden	3.49 (2.27, 4.89)	0.08 (0.00, 0.32)	N/A
Israel	N/A		
Western Australia		Not Converged	
Nordic Countries Combined	5.11 (3.36, 7.15)	0.01 (0.00, 0.25)	N/A
Model 3: A + C + M + E			
Country Specific			
Denmark	3.66 (2.38, 5.13)	0.01 (0.00, 0.43)	0.26 (0.10, 0.65)
Finland	N/A		
Sweden	3.99 (2.59, 5.58)	0.03 (0.00, 0.34)	0.03 (0.00, 0.33)
Israel	N/A		
Western Australia	N/A		
Nordic Countries Combined	4.84 (3.14, 6.36)	0.01 (0.00, 0.16)	0.04 (0.00, 0.21)

Notes:
CI: confidence interval; Nordic Countries: Denmark, Finland, Sweden; N/A: not applicable.
Variance component for non-shared environmental effect (E) is not shown in the table as it was set to be 1.
Data from Israel was not used for AD analyses because AD diagnosis was not available.

eTable 14. Autism Spectrum Disorder (ASD): Liability Model (**ACE**) Estimates - Fixed Parameters.

Model	**Covariates (95% CI)**		
	Sex (Female as reference)	**Birth Cohort** (2003-2007 vs. 1998-2002)	**Country** (Denmark as reference)
Country Specific			
Denmark	0.50 (0.49, 0.51)	-0.21 (-0.22, -0.20)	N/A
Finland	0.44 (0.42, 0.45)	-0.22 (-0.24, -0.20)	N/A
Sweden	0.40 (0.39, 0.41)	-0.24 (-0.25, -0.23)	N/A
Israel	0.51 (0.48, 0.55)	0.08 (0.04, 0.13)	N/A
Western Australia	0.46 (0.42, 0.49)	-0.15 (-0.20, -0.11)	N/A
Nordic Countries Combined			
Denmark	0.44 (0.43, 0.44)	-0.23 (-0.24, -0.22)	N/A
Finland			-0.32 (-0.33, -0.30)
Sweden			-0.00 (-0.01, 0.01)

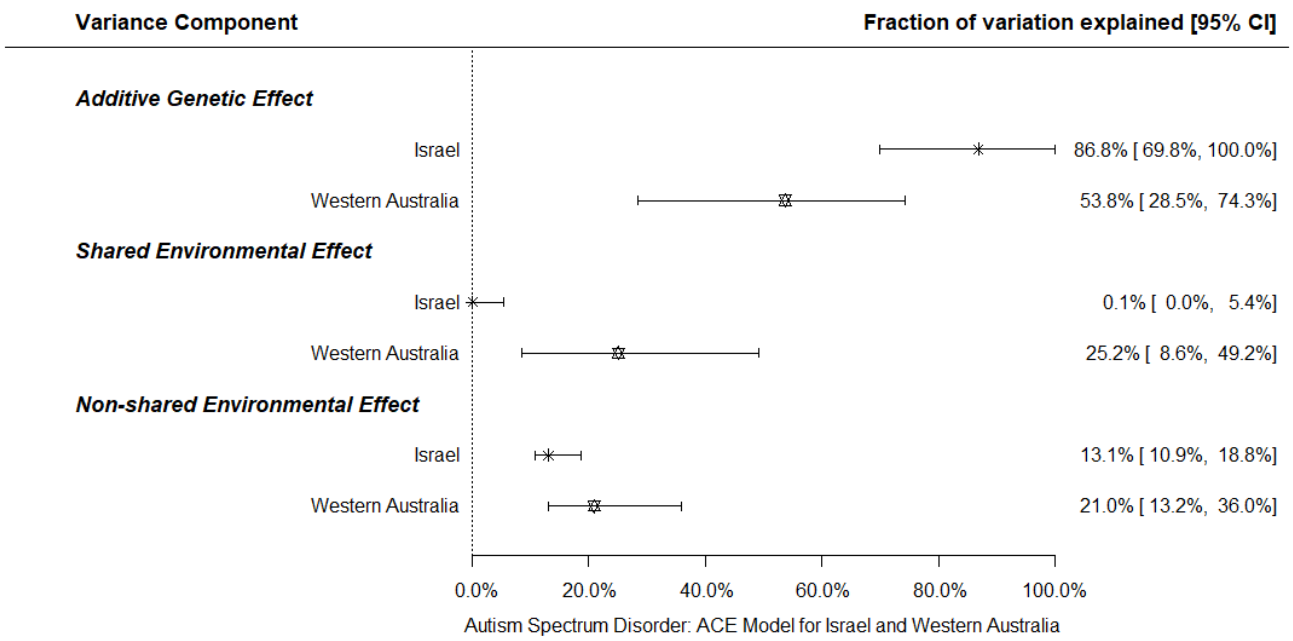
Notes:
CI: confidence interval; N/A: not applicable.
For Israeli cohort, the birth years were from 2000 to 2011, the comparison was conducted between 2006-2011 vs. 2000-2005.

eTable 15. Autistic Disorder (AD): Liability Model (**ACE**) Estimates - Fixed Parameters.

Model	**Covariates (95% CI)**		
	Sex (Female as reference)	**Birth Cohort** (2003-2007 vs. 1998-2002)	**Country** (Denmark as reference)
Country Specific			
Denmark	0.46 (0.44, 0.47)	-0.06 (-0.08, -0.05)	N/A
Finland	0.44 (0.42, 0.45)	-0.22 (-0.24, -0.20)	N/A
Sweden	0.38 (0.36, 0.38)	-0.09 (-0.10, -0.08)	N/A
Western Australia	Not Converged		
Nordic Countries Combined			
Denmark	0.40 (0.39, 0.41)	-0.09 (-0.09, -0.08)	N/A
Finland			-0.40 (-0.42, -0.39)
Sweden			-0.04 (-0.04, 0.05)

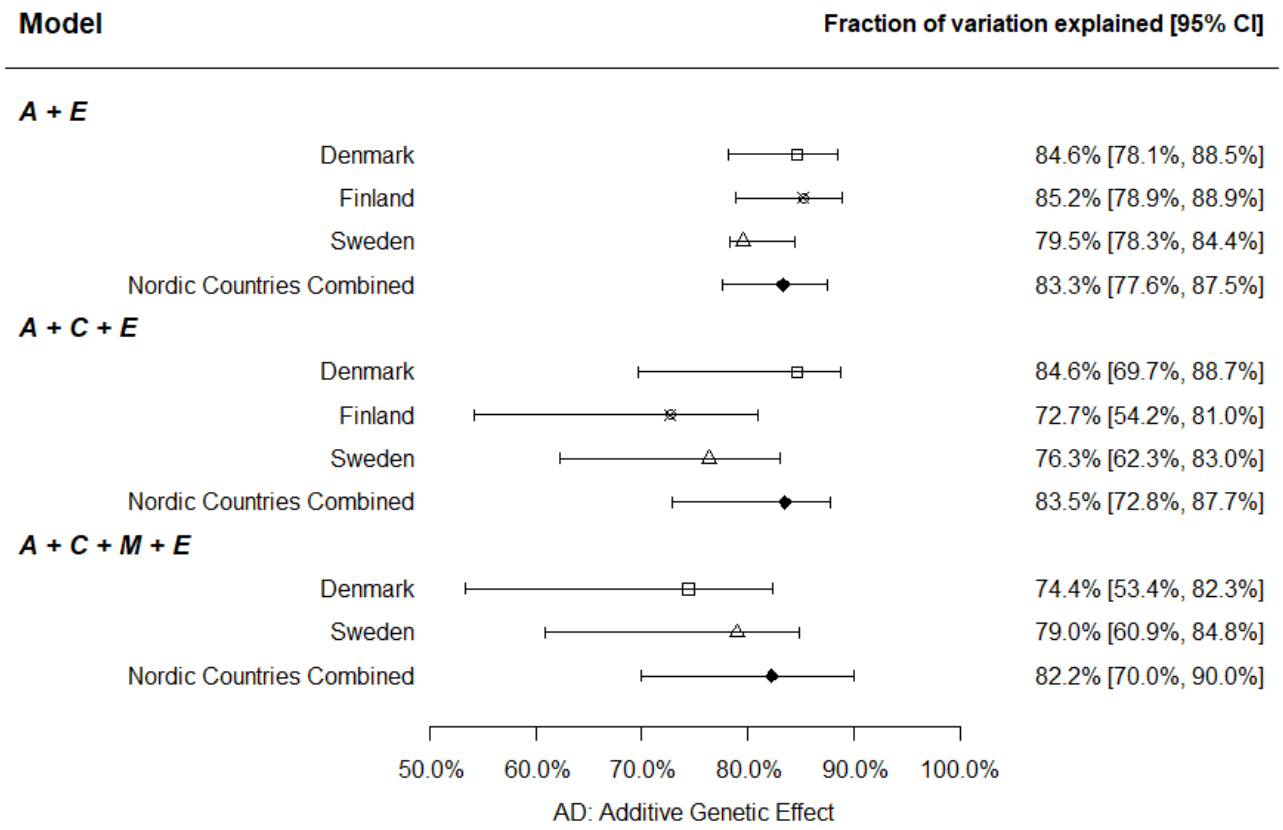
Notes:
CI: confidence interval; N/A: not applicable.
Data from Israel was not used for AD analyses because AD diagnosis was not available.

eFigure 6. Autism Spectrum Disorder (ASD): Variance Component Estimates (Two-sided 95% Profile Likelihood Confidence Interval), Recalculated to 'Fraction of Variation Explained'. ACE Model for Israel and Western Australia.



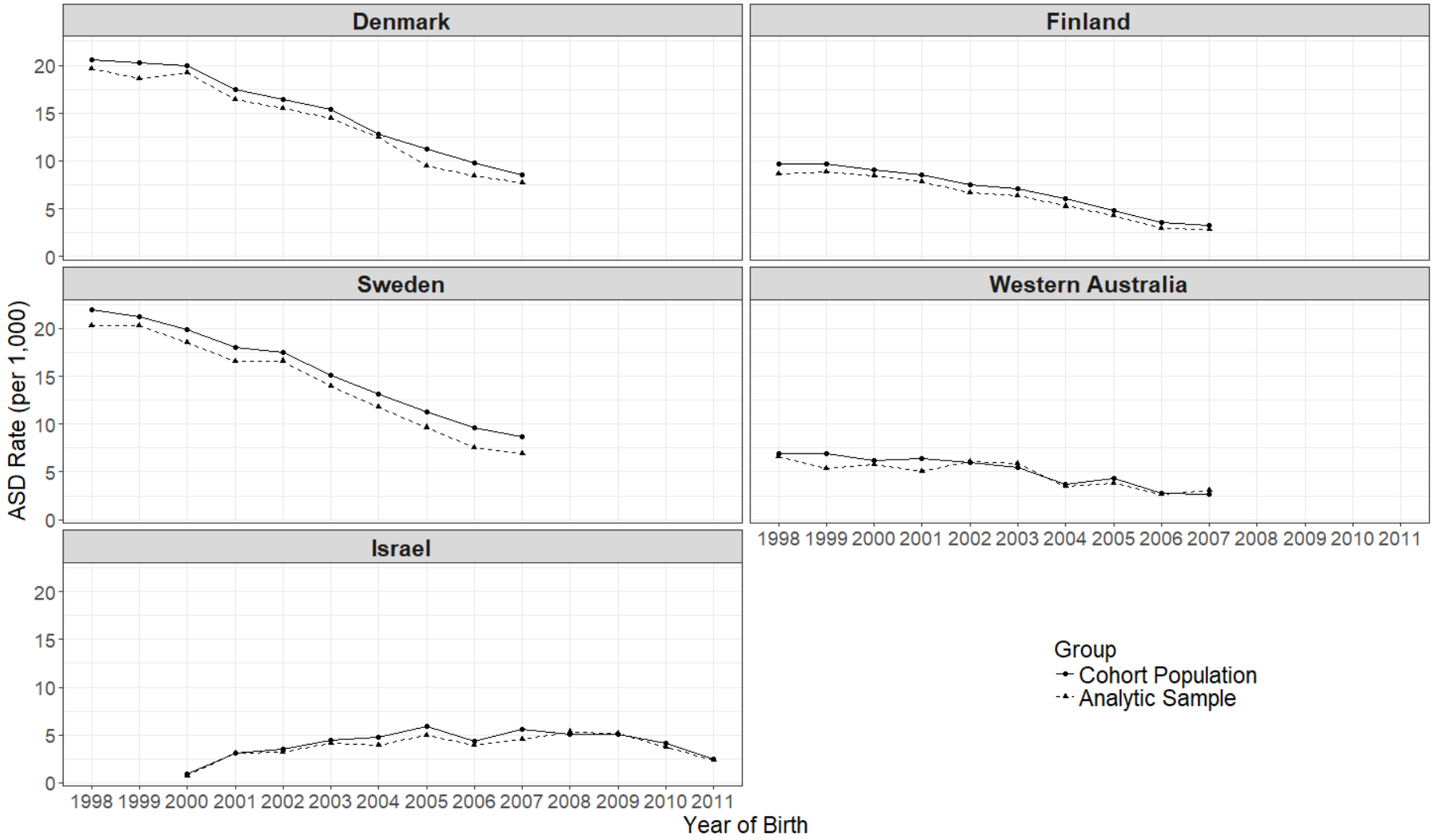
Notes: CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect.

eFigure 7. Autistic Disorder (AD): Estimated Additive Genetic Effect (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Recalculated to 'Fraction of Variation Explained'.

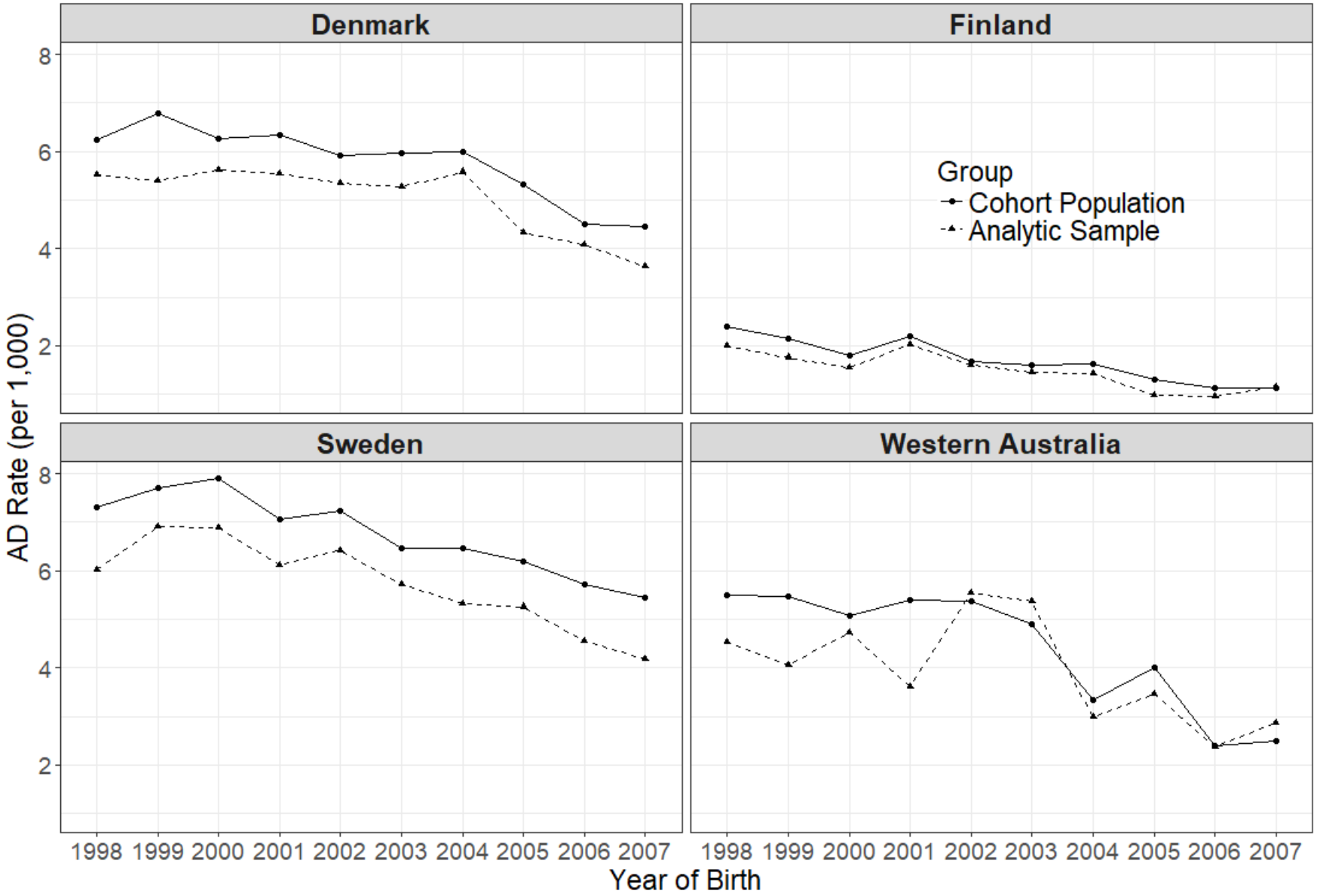


Notes: CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect.

eFigure 8. Autism Spectrum Disorder (ASD): Probability vs. Birth Year for the Cohort Population (Dotted Line) and the Analytic Sample (Solid Line).

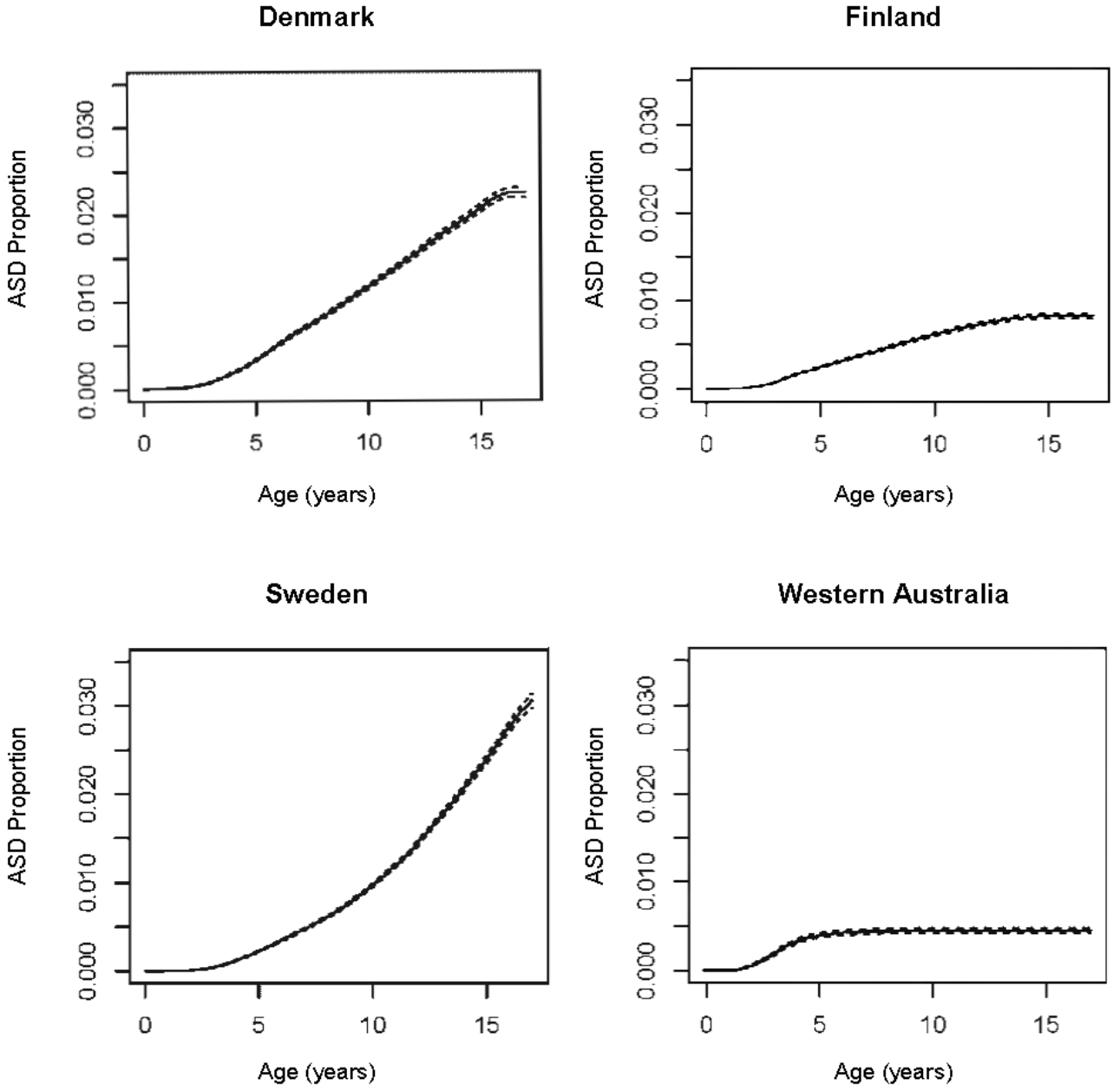


eFigure 9. Autistic Disorder (AD): Rate (per 1,000) vs. Birth Year for the Cohort Population (Dotted Line) and the Analytic Sample (Solid Line).



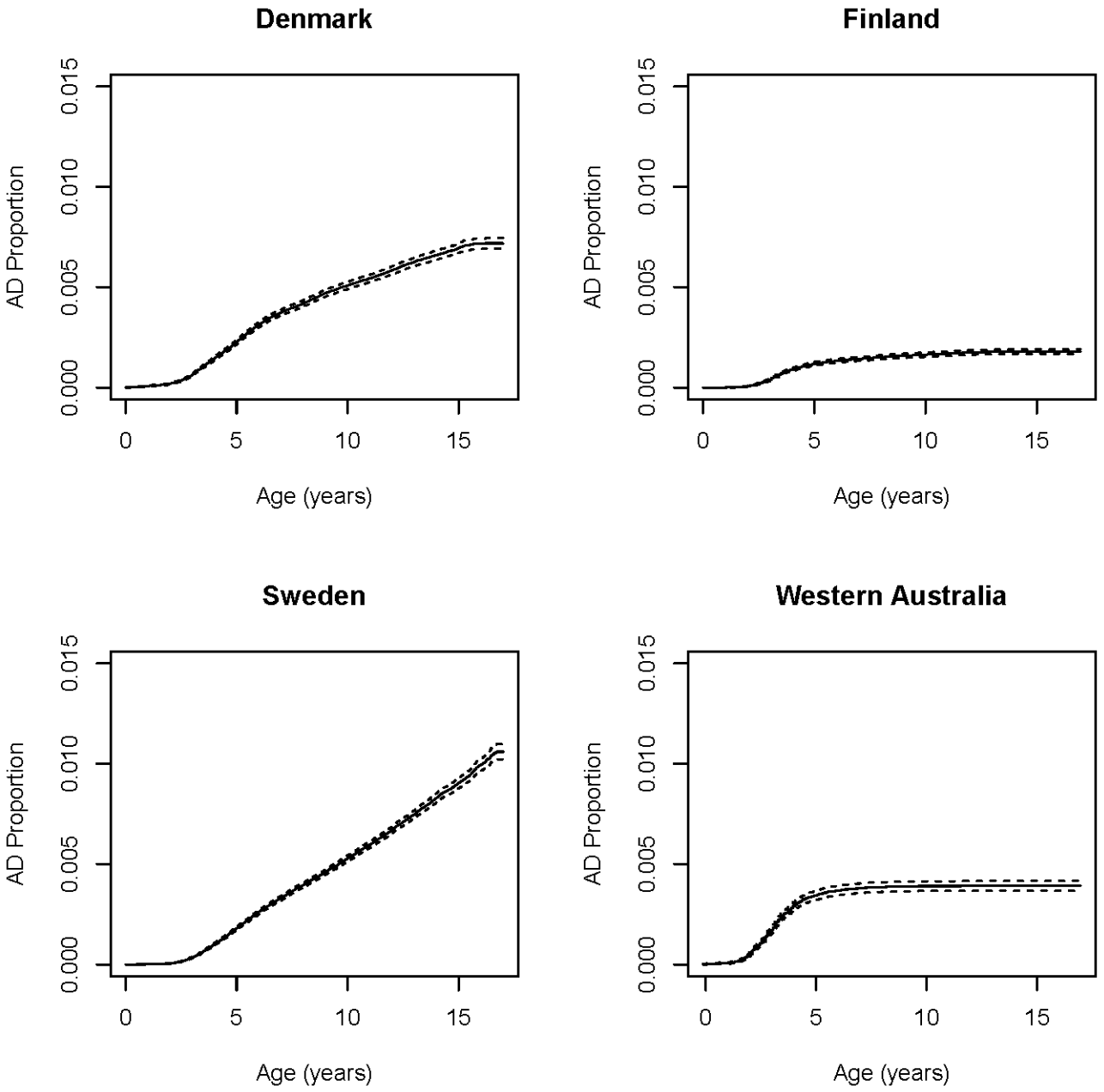
Note: Data from Israel was not used for AD analyses because AD diagnosis was not available.

eFigure 10. Autism Spectrum Disorder (ASD): Country Specific Inverse Kaplan-Meier Curve vs. Age (Years).



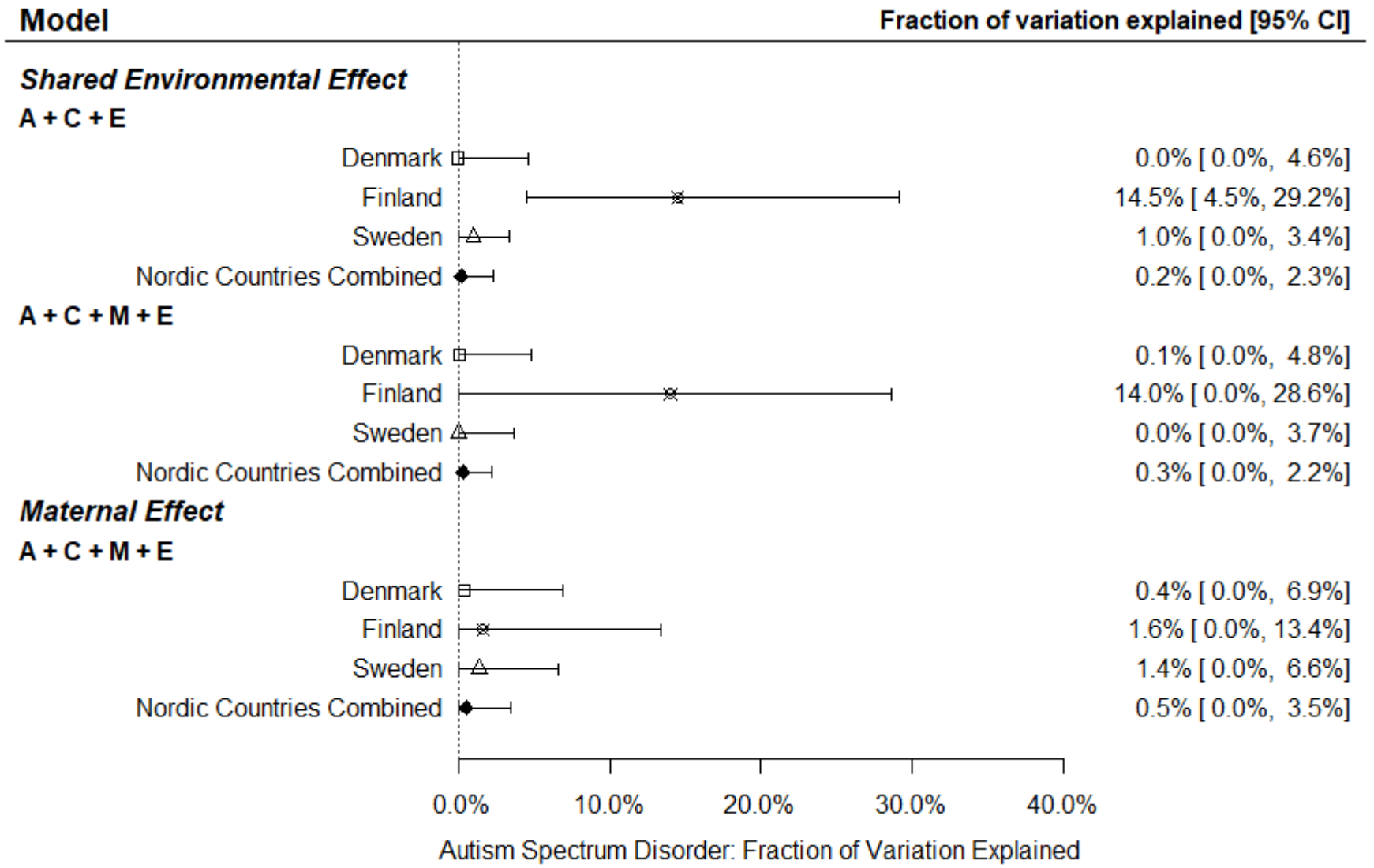
Note: Data from Israel was not used because year of diagnosis was not available.

eFigure 11. Autistic Disorder (AD): Country Specific Inverse Kaplan-Meier Curve vs. Age (Years).



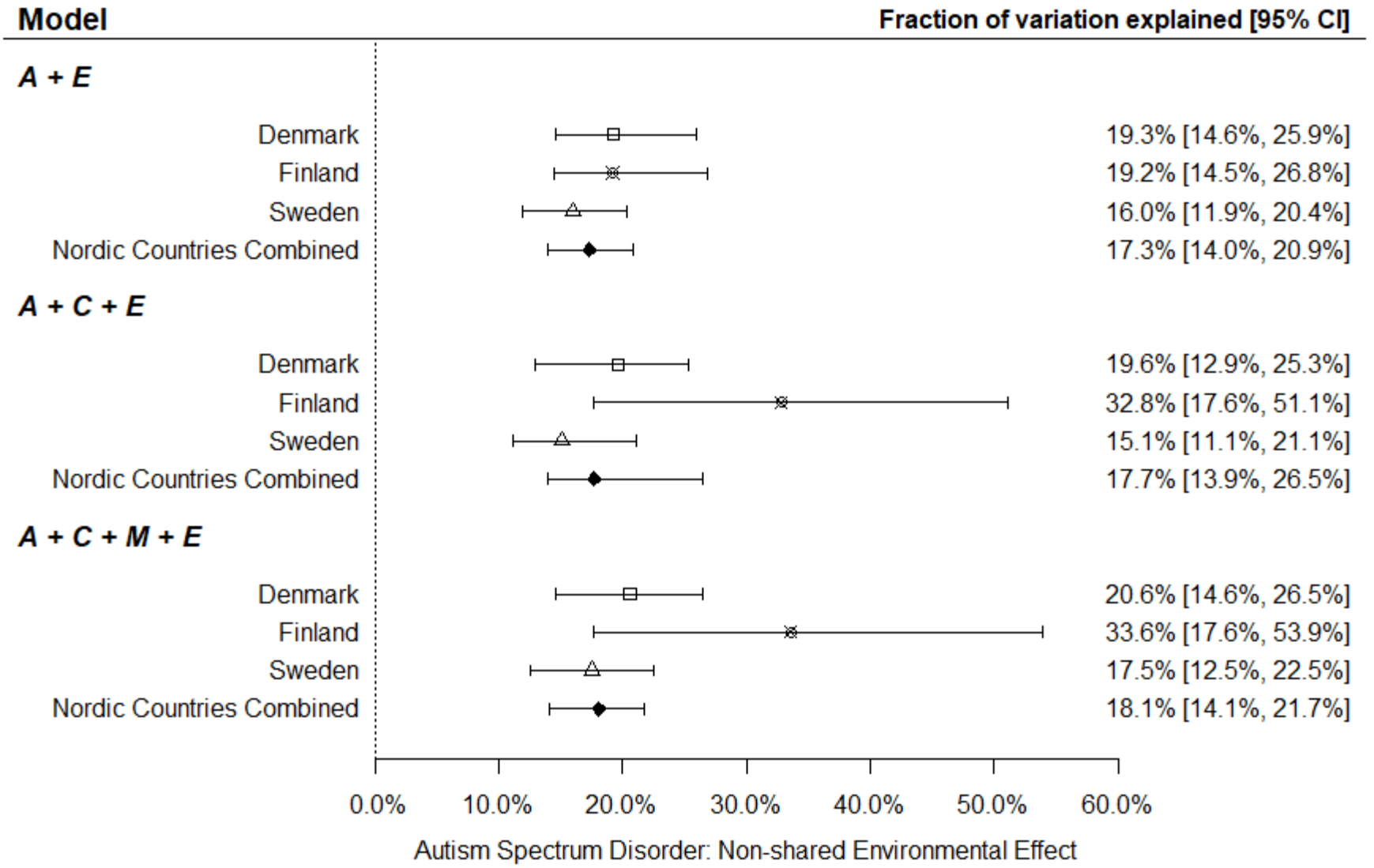
Note: Data from Israel was not used for AD analyses because AD diagnosis was not available.

eFigure 12. Autism Spectrum Disorder (ASD): Estimated Shared Environmental and Maternal Effect (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Are Recalculated to 'Fraction of Variation Explained'.



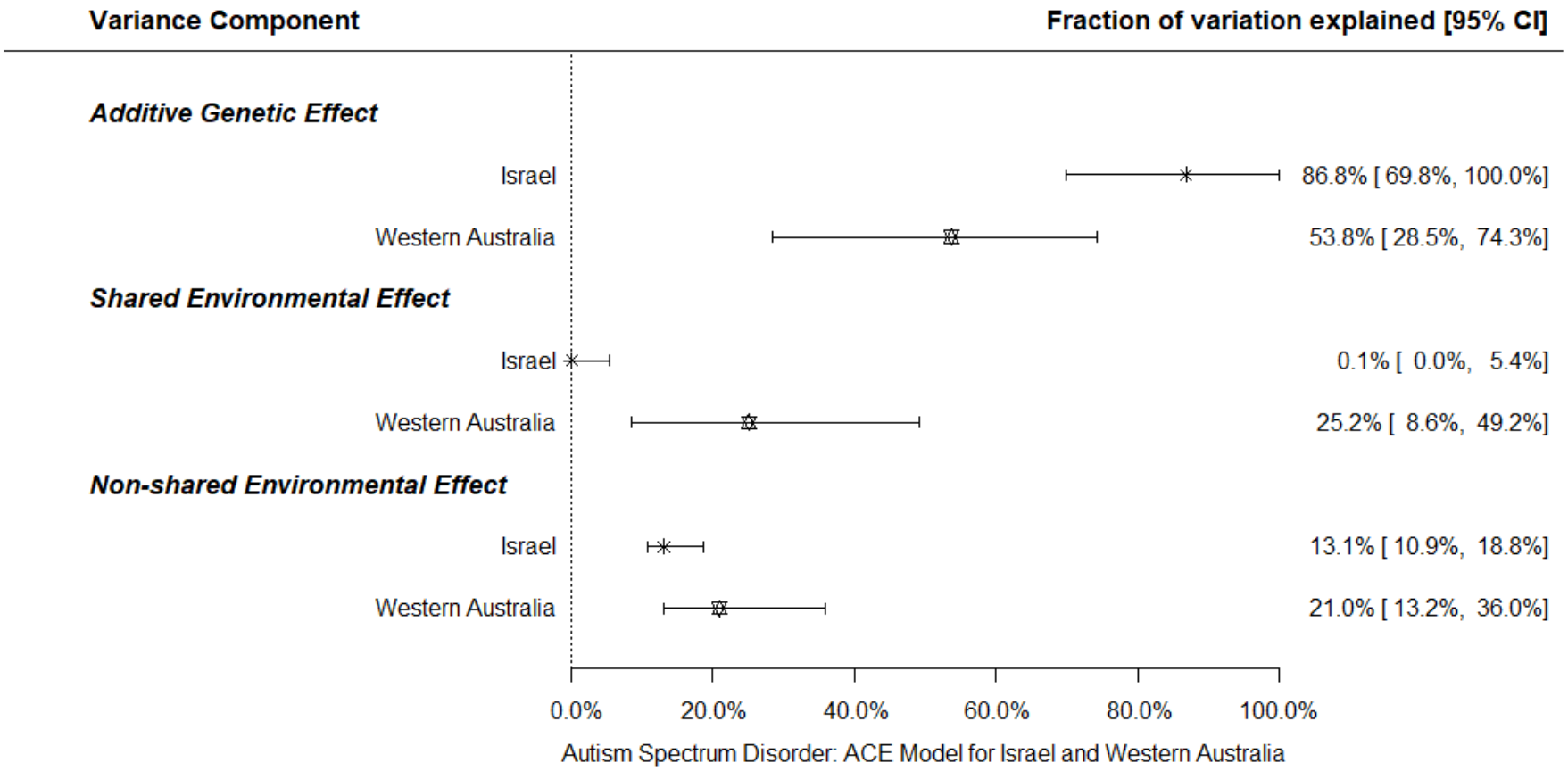
Notes: CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect.

eFigure 13. Autism Spectrum Disorder (ASD): Estimated Non-shared Environmental Effect (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Are Recalculated to 'Fraction of Variation Explained'.



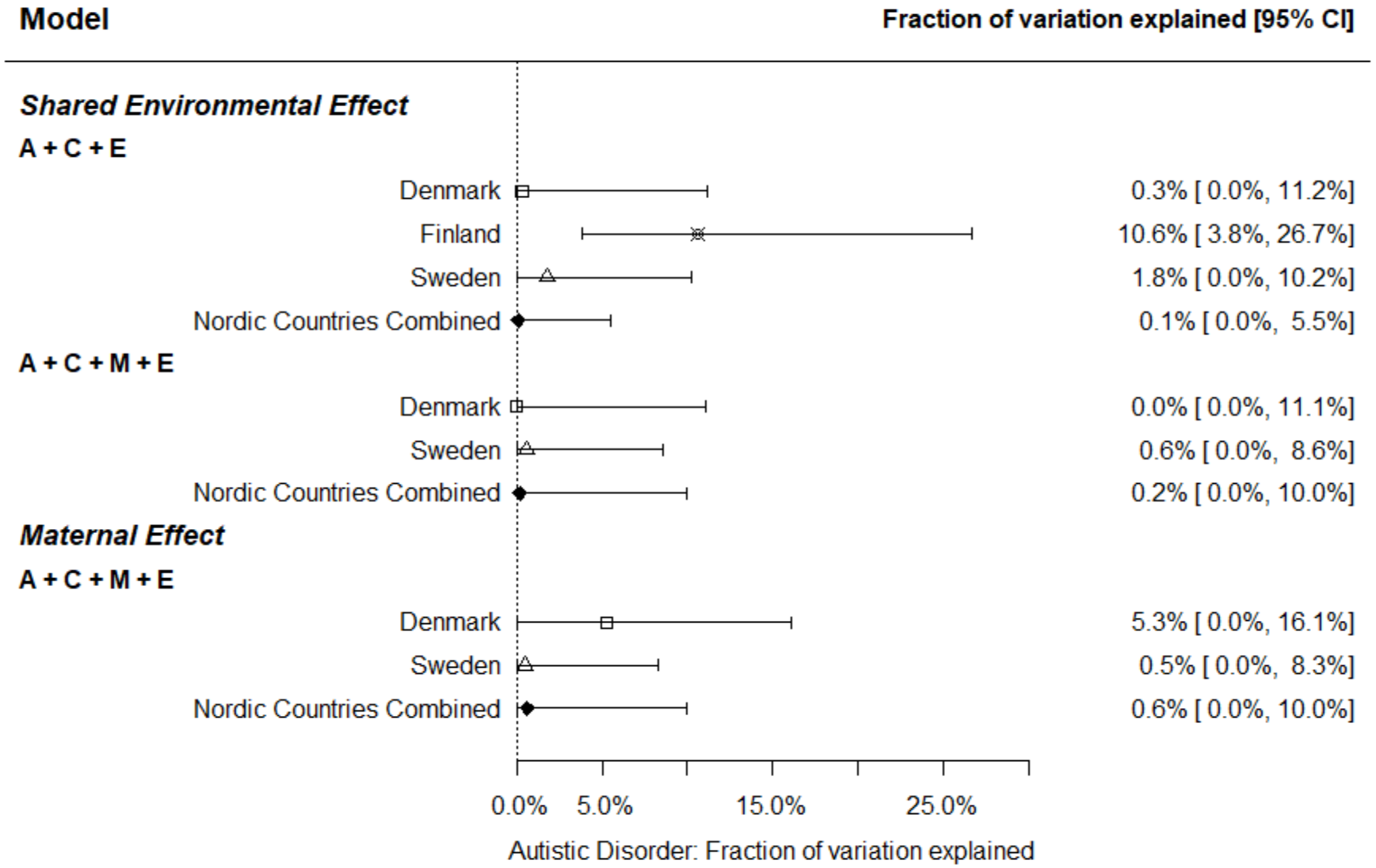
Notes: CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect.

eFigure 14. Autism Spectrum Disorder (ASD): Estimated Variance Components (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Are Recalculated to 'Fraction of Variation Explained'. **ACE** model for Israel and Western Australia.



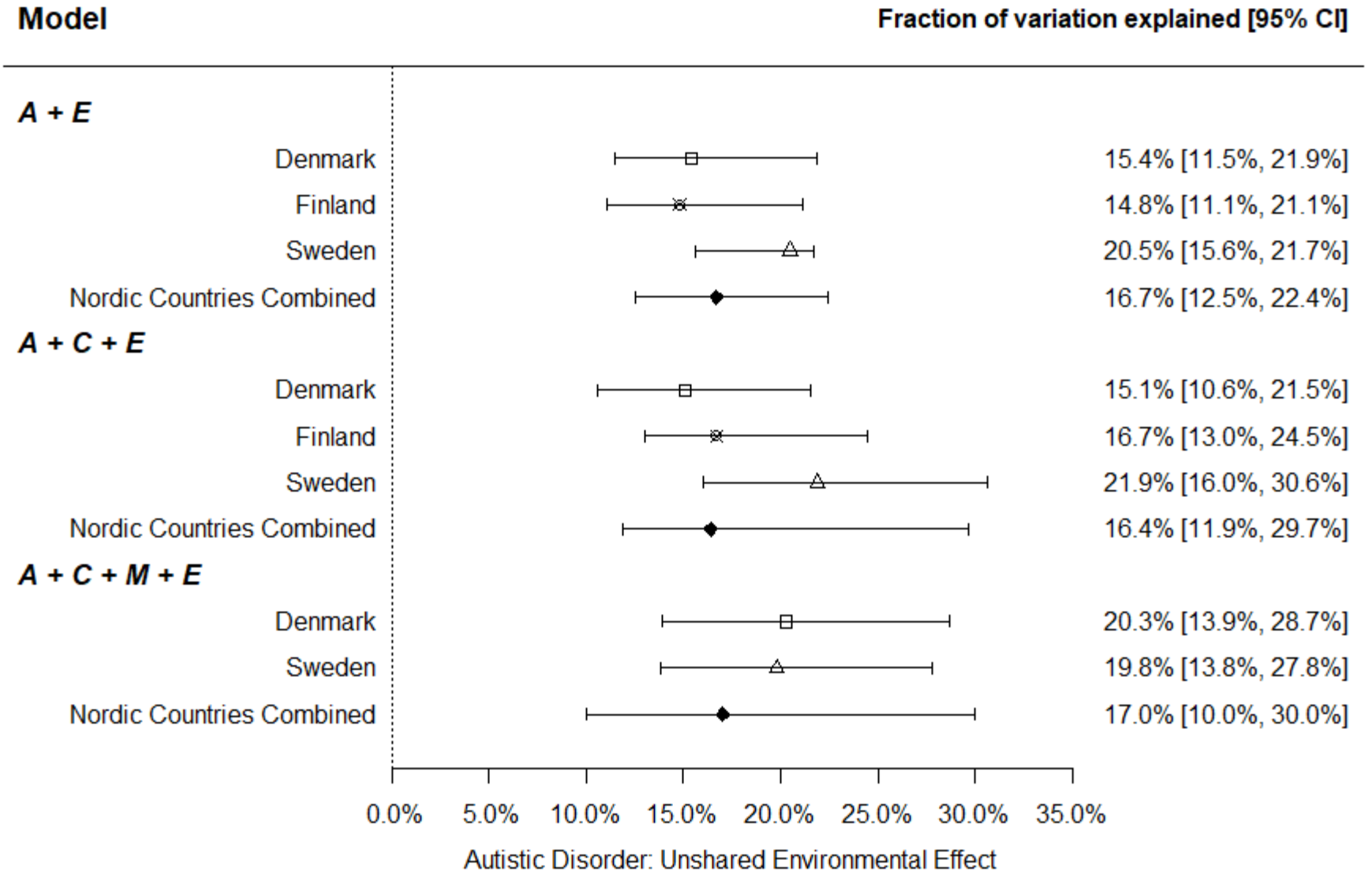
Note: CI: confidence interval.

eFigure 15. Autistic Disorder (AD): Estimated Shared Environmental and Maternal Effect (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Are Recalculated to 'Fraction of Variation Explained'.



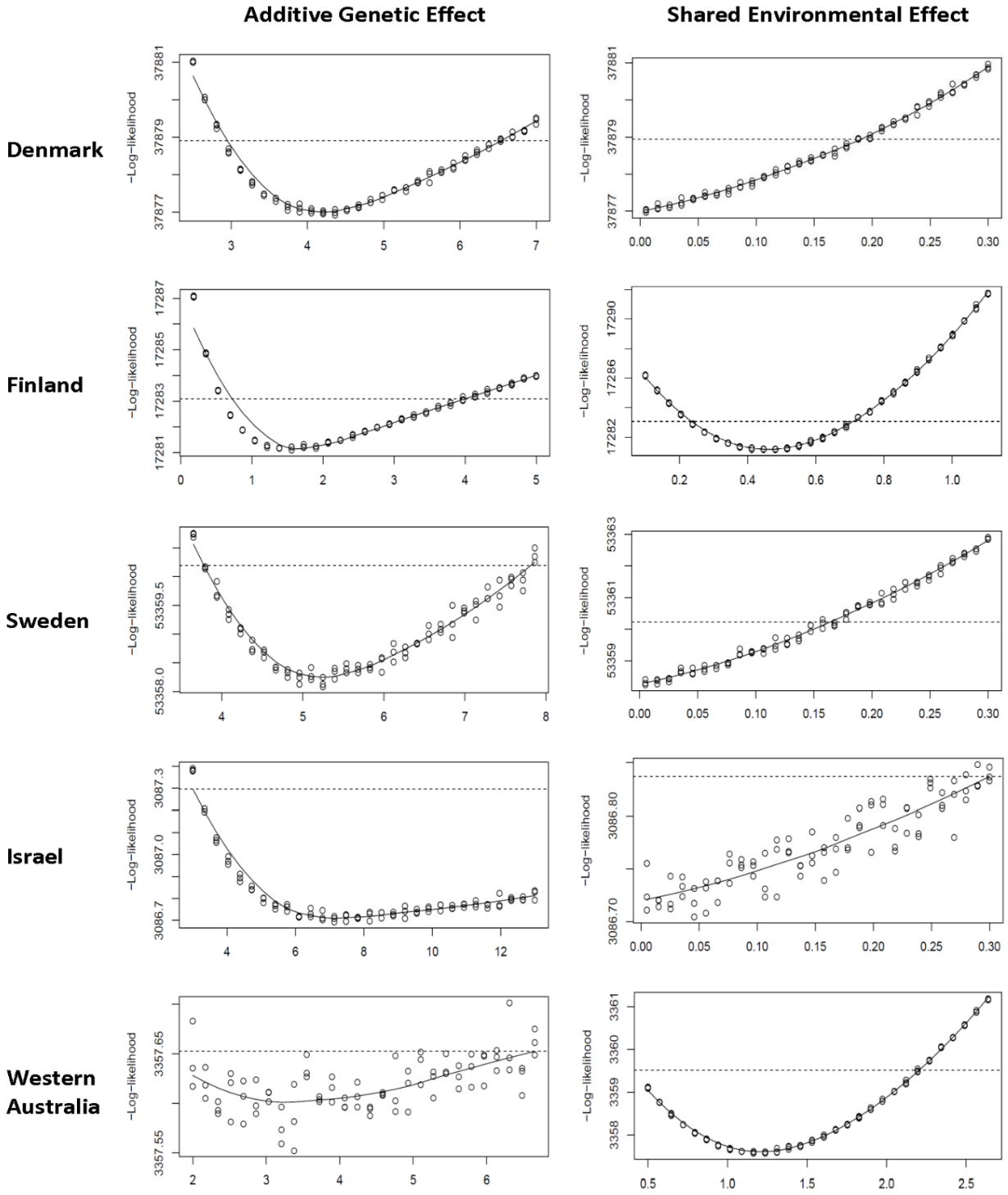
Notes: WA: Western Australia; CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect. WA was not presented in the figure because the AE and ACME models did not converge. Israel was not included for AD analyses because AD diagnosis was not available.

eFigure 15. Autistic Disorder (AD): Estimated Non-shared Environmental Effect (Two-sided 95% Profile Likelihood Confidence Interval). All Estimates Are Recalculated to 'Fraction of Variation Explained'.



Notes: WA: Western Australia; CI: confidence interval; A: additive genetic effect; C: shared environmental effect; M: maternal effect; E: non-shared environmental effect. WA was not presented in the figure because the AE and ACME models did not converge. Israel was not included for AD analyses because AD diagnosis was not available.

eFigure 16. Likelihood Functions for the Additive Genetic (A) and Shared Environmental (C) Effect in the **ACE** Model for Autism Spectrum Disorder (ASD).



Notes:
The exact numbers for the confidence intervals are found in **eTable 12**.
Crossing between likelihood function and the vertical dotted reference line give the two-sided 95% profile likelihood confidence intervals.

References

1. Steffenburg S, Gillberg C, Hellgren L, et al. A TWIN STUDY OF AUTISM IN DENMARK, FINLAND, ICELAND, NORWAY AND SWEDEN. *Journal of Child Psychology and Psychiatry and Allied Disciplines.* 1989;30(3):405-416.
2. Bailey A, Lecouteur A, Gottesman I, et al. AUTISM AS A STRONGLY GENETIC DISORDER - EVIDENCE FROM A BRITISH TWIN STUDY. *Psychol Med.* 1995;25(1):63-77.
3. Le Couteur A, Bailey A, Goode S, et al. A broader phenotype of autism: the clinical spectrum in twins. *J Child Psychol Psychiatry.* 1996;37(7):785-801.
4. Ronald A, Happe F, Bolton P, et al. Genetic heterogeneity between the three components of the autism spectrum: A twin study. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2006;45(6):691-699.
5. Taniai H, Nishiyama T, Miyachi T, Imaeda M, Sumi S. Genetic influences on the broad spectrum of autism: study of proband-ascertained twins. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147b(6):844-849.
6. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiat.* 2010;167(11):1357-1363.
7. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry.* 2011;68(11):1095-1102.
8. Nordenbaek C, Jorgensen M, Ohm Kyvik K, Bilenberg N. A population-based twin study on Autism Spectrum Disorders. *European Child and Adolescent Psychiatry.* 2011;20:S146.
9. Frazier TW, Thompson L, Youngstrom EA, et al. A twin study of heritable and shared environmental contributions to autism. *Journal of Autism & Developmental Disorders.* 2014;44(8):2013-2025.
10. Colvert E, Tick B, McEwen F, et al. Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample. *JAMA psychiatry.* 2015;72(5):415-423.
11. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The heritability of autism spectrum disorder. *Jama.* 2017;318(12):1182-1184.
12. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The Familial Risk of Autism. *JAMA-J Am Med Assoc.* 2014;311(17):1770-1777.
13. Yip BHK, Bai D, Mahjani B, et al. Heritable Variation, With Little or No Maternal Effect, Accounts for Recurrence Risk to Autism Spectrum Disorder in Sweden. *Biol Psychiatry.* 2017.
14. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. *Nature Genet.* 2014;46(8):881-885.
15. Pettersson E, Lichtenstein P, Larsson H, et al. Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychol Med.* 2018:1-8.
16. Kumar SK, Feldman MW, Rehkopf DH, Tuljapurkar S. Limitations of GCTA as a solution to the missing heritability problem. *Proc Natl Acad Sci U S A.* 2016;113(1):E61-E70.
17. Levine SZ, Levav I, Goldberg Y, Pugachova I, Becher Y, Yoffe R. Exposure to genocide and the risk of schizophrenia: a population-based study. *Psychol Med.* 2016;46(4):855-863.
18. Ekbom A. The Swedish Multi-generation Register. In: Dillner J, ed. *Methods in Biobanking.* Vol 675. Totowa: Humana Press Inc; 2011:215-220.

19. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Danish Medical Bulletin.* 1998;45(3):320-323.
20. MunkJorgensen P, Mortensen P. The Danish Psychiatric Central Register. *Danish Medical Bulletin.* 1997;44(1):82-84.
21. Gissler MH, Jari Finnish health and social welfare registers in epidemiological research. *Norsk Epidemiologi.* 2004;14(1):113-120.
22. Langhoff-Roos J, Krebs L, Klungsøyr K, et al. The Nordic medical birth registers – a potential goldmine for clinical research. *Acta Obstet Gynecol Scand.* 2014;93(2):132-137.
23. Holman CDJ, Bass AJ, Rosman DL, et al. A decade of data linkage in Western Australia: strategic design, applications and benefits of the WA data linkage system. *Aust Health Rev.* 2008;32(4):766-777.
24. Leonard H, Glasson E, Bebbington A, et al. Application of Population-Based Linked Data to the Study of Intellectual Disability and Autism. In: Urbano RC, ed. *Using Secondary Datasets to Understand Persons with Developmental Disabilities and Their Families.* Vol 45. San Diego: Elsevier Academic Press Inc; 2013:281-327.
25. Sandin S, Schendel D, Magnusson P, et al. Autism risk associated with parental age and with increasing difference in age between the parents. *Mol Psychiatr.* 2016;21(5):693-700.
26. Gal G, Abiri L, Reichenberg A, Gabis L, Gross R. Time trends in reported autism spectrum disorders in Israel, 1986-2005. *J Autism Dev Disord.* 2012;42(3):428-431.
27. Israeli Ministry of Health. Diagnostic Practice Guidelines: Autism Spectrum Disorders. 2013.
28. Breslow NE, Clayton DG. Approximate Inference In Generalized Linear Mixed Models. *J Am Stat Assoc.* 1993;88(421):9-25.
29. Pawitan Y, Reilly M, Nilsson E, Cnattingius S, Lichtenstein P. Estimation of genetic and environmental factors for binary traits using family data. *Stat Med.* 2004;23(3):449-465.
30. Yip BHK, Bai D, Mahjani B, et al. Heritable variation, with little or no maternal genetics contribution, accounts for recurrence risk to autism spectrum disorder in Sweden. *Biol Psychiatry.* 2017.
31. Pawitan Y. *In All Likelihood: Statistical Modelling and Inference Using Likelihood.* OUP Oxford; 2001.
32. Yip BH, Bjork C, Lichtenstein P, Hultman CM, Pawitan Y. Covariance component models for multivariate binary traits in family data analysis. *Stat Med.* 2008;27(7):1086-1105.
33. Noh M, Yip B, Lee Y, Pawitan Y. Multicomponent variance estimation for binary traits in family-based studies. *Genet Epidemiol.* 2006;30(1):37-47.
34. Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. Familial Recurrence of Autism Spectrum Disorder: Evaluating Genetic and Environmental Contributions. *Am J Psychiat.* 2014;171(11):1206-1213.
35. *R: A Language and Environment for Statistical Computing* [computer program]. Vienna, Austria2015.
36. Dowle M, Srinivasan A, Short T, Lianoglou S, with contributions from R Saporta and E Antonyan. data.table: Extension of Data.frame. 2015; R package version 1.9.6. Available at: http://CRAN.R-project.org/package=data.table.
37. Wickham H. Reshaping Data with the reshape Package. *Journal of Statistical Software.* 2007;21(12):1-20.
38. Bates D, Maechler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software.* 2015;67(1):1-48.

39. Genz A, Bretz F. Computation of Multivariate Normal and t Probabilities. *Lecture Notes in Statistics.* Vol 195. Heidelberg: Springer-Verlag; 2009.
40. Genz A, Bretz F, Miwa T, et al. mvtnorm: Multivariate Normal and t Distributions. R package version 1.0-3. 2015; http://CRAN.R-project.org/package=mvtnorm.
41. Therneau TM. A Package for Survival Analysis in S, version 2.38. 2015; https://CRAN.R-project.org/package=survival.
42. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model.* Springer; 2000.
43. Wickham H. *ggplot2: Elegant Graphics for Data Analysis.* New York: Springer-Verlag 2009.
44. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait - Evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry.* 2003;60(12):1187-1192.
45. Tick B, Bolton P, Happe F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. *J Child Psychol Psychiatry.* 2016;57(5):585-595.

